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Task Order No.: UIC-12A
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Title Page

Study Report for Task Order No. UIC-12A

FOUR WEEK TOXICITY STUDY OF WR279396 AFTER DAILY DERMAL APPLICATION IN CD® RATS

Sponsor: US Army Medical Materiel Development Activity

Test Article: WR279396

Contract No.: DAMD17-92-C-2001

Study Director

Barry S. Levine, D.Sc., D.A.B.T.

In-Life Phase Completed On

March 24, 1995

Performing Laboratory

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This study evaluated the toxicity of WR279396 (Iowa Formulation 232 containing 15% paromomycin sulfate and 0.5% gentamicin sulfate) in CD® rats following four weeks of daily dermal application. Three groups, each composed of 10 rats/sex, were initially given the test article twice daily by dermal application for the first five days. The volume of WR279396 administered per application (2 applications/day) were 0.07, 0.33, and 1.67 ml/kg, respectively, in low, mid and high dose animals. This corresponds to doses of 20, 100 and 500 mg/kg/day of paromomycin + 0.7, 3.3, 16.7 mg/kg/day of gentamicin, respectively. A control group of 10 male and 10 female rats received the test article vehicle (WR279396-Placebo, Iowa Formulation 232) by dermal application at a dosing volume of 1.67 ml/kg per application. Due to the appearance of moderate to severe erythema in mid and high dose animals on days 4 and 5, the volume (amount) of test article or vehicle control article administered was reduced to one-half the initial dose levels beginning on day 6 and for the remainder of the study. On day 6 and thereafter, test article volume (amount) was administered once daily instead of as a split dose twice daily. Following reduction in dosing frequency, very slight erythema (draize score = 1, barely perceptible), not accompanied by edema formation, was seen in most high dose animals. Acanthosis, thickening of the stratum spinosum layer of the epidermis, was also observed in several high dose animals and was generally of minimal severity. Except for one mid dose male, these dermal histologic changes were not seen at lower dosing volumes of WR279396, *i.e.* 0.33 or 0.07 ml/kg/day. Clinical signs, body weights, food intake, clinical chemistry and hematology parameters, ophthalmology evaluations and organ weights were not affected by test article treatment in any of the dose levels tested. A no-observed effect level (NOEL) was considered to be at or near 0.33 ml/kg/day of WR279396 administered once daily, corresponding to 50 mg/kg/day paromomycin + 3.3 mg/kg/day gentamicin in Iowa Formulation 232. However, more frequent application of test article per day at lower dosing volumes (*i.e.* 0.33 or 0.07 ml/kg) results in dermal irritation and potentially histologic changes in the skin at the exposure site.

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STATEMENT OF COMPLIANCE

To the best of my knowledge, Study No. 176 entitled "Four Week Toxicity Study of WR279396 after Daily Dermal Application in CD® Rats" was conducted in compliance with the Good Laboratory Practices regulations as published in 21 CFR 58, 40 CFR 160 and 40 CFR 792 in all material aspects with the following reservations.

The identity, strength, purity and composition or other characteristics to define the test or control articles have not been determined by the testing facility.

The stability of the test article or control article under the test conditions has not been determined by the testing facility.

Analyses to determine the uniformity, concentration, or stability of the test or control mixtures were not performed by the testing facility.

The protocol for this study was approved by the UIC Animal Care Committee.

Signature

Study Director

Barry S. Levine, D.Sc., D.A.B.T.

10/3/95
Date

QUALITY ASSURANCE STATEMENT

STUDY TITLE: FOUR WEEK TOXICITY STUDY OF WR279396 AFTER DAILY DERMAL APPLICATION IN CD® RATS

STUDY NUMBER: 176

STUDY DIRECTOR: BARRY S. LEVINE

INITIATION DATE: 10/28/94

This study has been divided into a series of phases. Using a random sampling approach, Quality Assurance personnel monitors each of these phases over a series of studies. Procedures, equipment, documentation, etc., are examined in order to assure that the study is performed in accordance with the Good Laboratory Practice regulations of the Food and Drug Administration and the Environmental Protection Agency to assure that the study is conducted according to the protocol.

The following are the inspection dates, phases inspected, and report dates of QA inspections of the study.

INSPECT ON 10/28/94, TO STUDY DIR 10/28/94, TO MGMT 10/28/94
PHASES: PROTOCOL REVIEW

INSPECT ON 2/22/95, TO STUDY DIR 2/24/95, TO MGMT 2/27/95
PHASES: ROOM ENVIRONMENT

INSPECT ON 2/23/95, TO STUDY DIR 2/24/95, TO MGMT 2/27/95
PHASES: DOSING, BODY WEIGHT, FOOD CONSUMPTION AND CLINICAL SIGNS

INSPECT ON 3/23/95, TO STUDY DIR 3/24/95, TO MGMT 3/24/95
PHASES: BLOOD COLLECTION, CLINICAL PATHOLOGY AND MICROCHIP IDENTIFICATION SCANNING

INSPECT ON 4/26-27/95, TO STUDY DIR 4/27/95, TO MGMT 5/1/95
PHASES: RAW DATA

INSPECT ON 6/22-23/95, TO STUDY DIR 6/23/95, TO MGMT 6/23/95
PHASES: PATHOLOGY DRAFT REPORT

INSPECT ON 6/26/95, TO STUDY DIR 6/26/95, TO MGMT 6/27/95
PHASES: DRAFT REPORT

INSPECT ON 10/3/95, TO STUDY DIR 10/3/95, TO MGMT 10/3/95
PHASES: FINAL REPORT

Ronald Rohrbeck 10/3/95

QUALITY ASSURANCE DATE

Signature Page

FOUR WEEK TOXICITY STUDY OF WR279396 AFTER DAILY DERMAL APPLICATION IN CD® RATS

Test Article.: WR279396

Sponsor: US Army Medical Materiel
Development Activity
Fort Detrick
Frederick, MD 21702-5009

Sponsor
Representative: George J. Schieferstein, Ph.D.

Testing Facility: TOXICOLOGY RESEARCH LABORATORY (TRL)
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Barry S. Levine, D.Sc., D.A.B.T. — Date
Study Director

Clyde W. Wheeler — 10/3/95

Clyde W. Wheeler, Ph.D. — Date
Toxicologist

Study Initiation: October 28, 1994
Dosing Initiation: February 23, 1995
In-Life Completion: March 24, 1995

TABLE OF CONTENTS

TITLE PAGE 1

STATEMENT OF COMPLIANCE 2

QUALITY ASSURANCE STATEMENT 3

SIGNATURE PAGE 4

TABLE OF CONTENTS 5

1. SUMMARY 7

2. INTRODUCTION 7

3. MATERIALS AND METHODS 8

3.1 Test Article 8
3.2 Placebo (Vehicle) 8
3.3 Animals 8
3.4 Experimental Design 9
3.5 Statistical Analyses 13

4. RESULTS 13

4.1 Mortality and Clinical Signs 13
4.2 Dermal Irritation Evaluations 13
4.3 Body Weights 14
4.4 Food Consumption 14
4.5 Clinical Pathology 14
4.6 Ophthalmology 15
4.7 Organ Weights 15
4.8 Pathology 15

5. DISCUSSION/CONCLUSION 16

6. PERSONNEL 17

7. ARCHIVES 17

8. REFERENCE 17

LIST OF TABLES

1 Summary of Toxic Responses 18
2 Summary of Clinical Signs 19
3 Dermal Irritation Evaluation 21

TABLE OF CONTENTS (contd.)

LIST OF TABLES (contd.)

4 Summary of Body Weights 25
5 Summary of Weight Gains 27
6 Summary of Daily Food Consumption 29
7 Summary of Clinical Chemistry Tests 31
8 Summary of Hematology Tests 35
9 Organ Weight Summary (% Brain Weight) 39
10 Summary of Microscopic Lesions 41

FIGURES

1 Summary of Male Body Weights 42
2 Summary of Female Body Weights 43

APPENDICES

1 Clinical Pathology Methodology 1-1
2 Individual Clinical Signs 2-1
3 Individual Body Weights and Body Weight Gains 3-1
4 Individual Food Consumption Data 4-1
5 Individual Clinical Chemistry Data 5-1
6 Individual Hematology Data 6-1
7 Ophthalmology Report 7-1
8 Individual Organ Weights 8-1
9 Pathology Report 9-1
10 Photographs of Treatment Sites on Day 6 10-1
11 Protocol and Protocol Amendments 11-1
12 Study Deviations 12-1

1. SUMMARY

This study evaluated the local and systemic (organ) toxicity of WR279396 (Iowa Formulation 232 containing 15% paromomycin sulfate and 0.5% gentamicin sulfate) in CD® rats following four weeks of daily dermal application. The results are summarized in Table 1. Three groups, each composed of 10 male and 10 female rats, were initially given the test article twice daily by dermal application for the first five days. The volume of WR279396 administered per application (2 applications/day) were 0.07, 0.33, and 1.67 ml/kg, respectively, in low, mid and high dose animals. This corresponds to doses of 20, 100 and 500 mg/kg/day of paromomycin + 0.7, 3.3, 16.7 mg/kg/day of gentamicin, respectively. A control group of 10 male and 10 female rats received the test article vehicle (WR279396-Placebo, Iowa Formulation 232) by dermal application at a dosing volume of 1.67 ml/kg per application. Due to the appearance of moderate to severe erythema in mid and high dose animals on days 4 and 5, the volume (amount) of test article or vehicle control article administered was reduced to one-half the initial dose levels beginning on day 6 and for the remainder of the study. On day 6 and thereafter, test article volume (amount) was administered once daily in the morning instead of as a split dose twice daily.

Following reduction in dosing frequency, very slight erythema (draize score = 1, barely perceptible), not accompanied by edema formation, was seen in most high dose animals. Acanthosis, thickening of the stratum spinosum layer of the epidermis, was also observed in several high dose animals and was generally of minimal severity. Except for one mid dose male, these dermal histologic changes were not seen at lower dosing volumes of WR279396, *i.e.* 0.07 or 0.33 ml/kg/day (dose of 20 and 100 mg/kg/day of paromomycin + 0.7 and 3.3 mg/kg/day of gentamicin, respectively). Clinical signs, body weights, food intake, clinical chemistry and hematology parameters, ophthalmology evaluations and organ weights were not affected by test article treatment in any of the dose levels tested. A no-observed effect level (NOEL) was considered to be at or near 0.33 ml/kg/day of WR279396 administered once daily, corresponding to 50 mg/kg/day paromomycin + 3.3 mg/kg/day gentamicin in Iowa Formulation 232. However, more frequent application of test article per day results in dermal irritation and potentially histologic changes in the skin at the exposure site. Following six days of treatment, the twice daily application of the volume of test article produced well-defined erythema in low dose animals and moderate to severe erythema in mid and high dose animals.

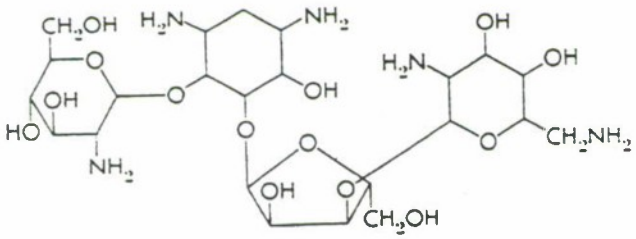
2. INTRODUCTION

This study was conducted to determine the local and systemic (organ) toxicity of WR279396 in CD® rats following four weeks of daily dermal application. The study was conducted in accordance with the specifications of the Sponsor as indicated in Task Order UIC-12. The rats used in the study are a standard and accepted rodent species for regulatory toxicology studies, and were specified by the Sponsor. Dermal application is the intended clinical route and was also specified by the Sponsor. All methods and procedures were conducted in accordance with the Quality Assurance Programs of the Toxicology Research Laboratory, University of Illinois at Chicago and Pathology Associates, Inc., designed to conform with FDA Good Laboratory Practices Regulations. No unforeseen circumstances affected the integrity of the study. Dosing was initiated on February 23, 1995 and the in-life portion was terminated on March 24, 1995.

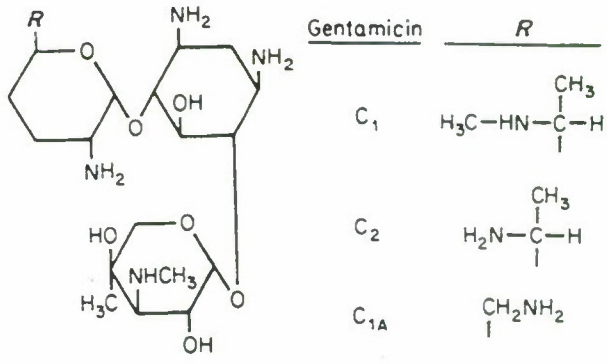
3. MATERIALS AND METHODS

3.1 Test Article

WR279396 (Bottle No. 42985, Lot No. WRAST02/161), a white cream, was received on January 20, 1995 from Herner & Co., and was assigned an in-house chemical number (1980614). The test article, Iowa Formulation 232 cream, contains 0.5% gentamicin sulfate and 15% paromomycin sulfate. As indicated by the Sponsor, the specific gravity of the test article cream is 1.0. It was stored at 2 to 8°C and ambient humidity, and protected from light in an opaque bottle. The chemical structures of paromomycin and gentamicin are shown below. As illustrated, gentamicin sulfate typically is a mixture of three related sulfate salts isolated from *Micromonospora purpurea*.



Paromomycin



Gentamicin

3.2 Placebo (Vehicle)

WR279396-Placebo (Bottle No. 42994, Lot No. WRAST02/162), a white cream, was received on January 20, 1995 from Herner & Co., and was assigned an in-house chemical number (1990614). The control article was Iowa Formulation 232 without gentamicin sulfate and paromomycin sulfate. It was stored at 2 to 8°C and ambient humidity, and protected from light in an opaque bottle.

3.3 Animals

Fifty male and fifty female CD® Virus Antibody Free (VAF) rats were obtained from Charles River Breeding Laboratories (Kingston, NY) on February 15, 1995. The animals were approximately 6 weeks old (date of birth January 2, 1995) upon arrival at the UIC AAALAC-accredited animal facility. Each animal was given a study-unique

quarantine/pretest number following placement in cages. Animals were singly housed in polycarbonate cages with Anderson bed-o-cob® bedding (Heinold, Kankakee, IL) in a temperature (65 - 78°F) and humidity (30 - 70%) controlled room with a 14 hour light/10 hour dark cycle. The cage size, 840 cm^2 area and 20 cm height, was adequate to house rats at the upper weight range as described in the *Guide for the Care and Use of Laboratory Animals*, DHHS (NIH) No. 86.23. All animals were routinely transferred to clean cages with fresh bedding weekly.

Certified Rodent Chow No. 5002 (PMI Inc., St. Louis, MO) was provided *ad libitum* from arrival until termination. Tap water from an automatic watering system in which the room distribution lines were flushed daily was provided *ad libitum*. The water was not treated with additional chlorine or HCl. There were no known contaminants in the feed or water which were expected to influence the study. The results of the most current comprehensive chemical analyses of Chicago water performed by the City of Chicago are documented in files maintained by Quality Assurance.

3.4 Experimental Design

All animals were examined daily during the eight day quarantine/pretest period, and were approved for use by the Clinical Veterinarian prior to being placed on test. Near the end of the quarantine/pretest period, 40 animals of each sex were randomized by sex into four groups shown in the following table using a computer-generated randomization program, stratified on the basis of body weight.

Treatment Group	Treatment	Paromomycin Dose Level (mg/kg/day)	Gentamicin Dose Level (mg/kg/day)	Dosing Volume (ml/kg/day)	Number of Males	Number of Females
1	Vehicle	0	0	1.67 x 2 (1.67)	10	10
2	WR279396	20 (10)	0.7 (0.04)	0.07 x 2 (0.07)	10	10
3	WR279396	100 (50)	3.3 (1.7)	0.33 x 2 (0.33)	10	10
4	WR279396	500 (250)	16.7 (8.4)	1.67 x 2 (1.67)	10	10

The initial and reduced dose levels were selected following discussions with the Sponsor. The reduced dose levels and dosing volumes (shown inside of parentheses) were chosen based upon the estimated dose which will be given to the patient. As indicated by the Sponsor, the intended routine clinical dose of paromomycin is 5 mg/kg/day. As such, a low dose of 10 mg/kg/day in this study allows for a two-fold margin of safety. It was further stated by the Sponsor that the maximum clinical dose for a severely infected individual would be 50 mg/kg/day. Accordingly, the mid dose (reduced dose level) duplicates this worst case scenario clinical dose. The high dose level in this study of 500 mg/kg/day (1.67 ml WR279396/kg/application) was intended to result in toxicity and was

near the typical upper limit of dermal dosing of 2 ml/kg/application.

Due to the appearance of localized moderate to severe erythema at the treatment site in mid and high animals on days 4 and 5, the dose levels were reduced by one-half after discussions with the Sponsor. Beginning on day 6 and for the remainder of the study, the frequency of treatment was reduced from twice daily to once daily. The dosing volume per application remained constant. The subsequent dose levels of paromomycin sulfate and gentamicin sulfate and the subsequent dosing volumes of test article are shown in the previous page in parentheses.

During the animal selection process, each animal was assigned an animal number unique to it within the population making up the study. This number appeared as an ear tag and was also coded on a subcutaneously implanted microchip. This number also appeared on a cage card visible on the front of each cage. The cage card additionally contained the study number, test article identification, sex, treatment group number, and dose level. Cage cards were color-coded as a function of treatment group.

On days 0 - 5, the test or control article cream was applied by the dermal route twice daily. As previously stated, beginning on day 6 and for the remainder of the study, the frequency of treatment was reduced to once daily. The fur on the back of each test animal was clipped approximately 24 hours prior to initial test article application. An area approximately 7 cm long and extending approximately 3 cm on both sides of the midline was exposed and constituted the dosing area. Only animals with healthy intact skin were used. The backs were reshaved during the course of the study as necessary.

On days -3 to -1, the animals were acclimated to a rodent jacket for dermal application (LOMIR Biomedical Inc., Malone, NY) for 6 - 8 hours each day. The dermal jacket included a plastic shield which extended over, but was not in contact with, the treatment site. Immediately prior to the initial treatment on day 0 and weekly thereafter, the dosing area was abraded by cross-hatched cuts made with a detached size 10 electric clipper blade so that the stratum corneum was penetrated but the dermis was left intact. The test article was administered using a 1 ml tuberculin syringe (0.01 ml graduations) and uniformly applied as a thin film over the exposure area of the skin (up to $\approx$ 10% of the total body surface area). It was applied twice daily on days 0 - 5, in the morning and afternoon, approximately 3 - 4 hours apart, or once daily in the morning beginning on day 6 for at least 28 consecutive days. The specific volume administered (to the nearest 0.01 ml) was adjusted on the basis of each animal's most recent body weight. The material was initially applied to a latex-gloved finger, which was used to uniformly apply the test article to the exposure area of the skin. A separate gloved finger was used for each animal, i.e. after dosing up to four rats, the glove was discarded, and a new latex glove was donned. The application site was left uncovered, however animals were immediately fitted in dermal jackets which prevented them from licking off the material. Approximately 3 - 4 hours after each application (either once daily, or twice daily on days 0 - 5), the exposure site was wiped with a water-moistened paper towel. On days 0 - 5, the test article or control article (vehicle) was applied a second time, as previously

described. Following the final daily application, the animal jackets were removed and left off overnight. The animals were dosed up to and including the day prior to scheduled necropsy on day 28 or 29.

Body weights were recorded at randomization on day -3, on day 0, and weekly thereafter. On days 0 - 5, clinical signs were observed and recorded for all animals twice daily, approximately 1 - 2 hours after each dermal application. The general behavior, posture, locomotion, breathing pattern and coat were observed in all animals. Clinical signs are indicated in the Summary of Clinical Signs (Tables 2.1 and 2.2) and Individual Clinical Signs (Appendix 2) as Clinical Sign 1 or 2, *i.e.* Normal 1st Sign and Normal 2nd Sign. Beginning on day 6, clinical signs were observed and recorded for all animals once daily, approximately 1 - 2 hours after dermal application, and are indicated in Tables 2.1 and 2.2 and Appendix 2 as Clinical Sign 1, *i.e.* Normal 1st Sign. The animals were also observed in the morning for moribundity/mortality. Physical examinations (clinical observations) which included examination of eyes and all orifices were conducted in week -1, on day 0, and weekly thereafter. Dermal irritation at the treatment site was evaluated on day 0 and weekly thereafter. The draize dermal irritation scoring procedure was employed (Draize, 1965). Food consumption was measured for all animals weekly commencing with week -1.

Hematology and clinical chemistry parameters were measured in all animals on days 27 and 28. The nonfasted animals were anesthetized by inhalation of CO_2:O_2 (70:30), and approximately 1.5 - 2.0 ml of blood were collected from the orbital sinus to measure the following parameters. The samples were processed in the same random order as collected. Clinical pathology methodology is contained in Appendix 1.

Hematology

- Erythrocyte count and morphology
- Hematocrit
- Hemoglobin
- Leukocyte count, total and differential
- Mean corpuscular hemoglobin (MCH)
- Mean corpuscular hemoglobin concentration (MCHC)
- Mean corpuscular volume (MCV)
- Platelet count
- Reticulocyte count

Clinical Chemistry

- Alanine aminotransferase (ALT)
- Albumin
- Alkaline phosphatase
- Bile acids, total
- Calcium
- Chloride
- Cholesterol
- Creatinine
- Glucose
- Globulin (calc.)
- Phosphorus, inorganic
- Potassium
- Protein, total
- Sodium
- Sorbitol dehydrogenase
- Urea nitrogen (BUN)

With the exception of one accidental death (animal no. 330, low dose male, which was necropsied on the day of its death), all animals were killed and necropsied in random order over a two consecutive day period (days 28 and 29). Animals were anesthetized by Metofane® inhalation (Pitman-Moore, Mundelein, IL) and then perfused transcardially with saline followed by 10% neutral buffered formalin (NBF). An extensive necropsy was performed under the direction and supervision of the pathologist. Terminal body weights were collected prior to routine sacrifice.

The necropsy procedure was a thorough and systematic examination and dissection of the animal viscera and carcass, and collection and fixation of the following tissues/organs in 10% neutral buffered formalin (NBF).

*Adrenal glands
Aorta
*Brain
Cecum
Colon
Duodenum
Ears (including sensory hair cells of *crista ampullaris*, cochlear and vestibular hair cells, and middle and inner ear)
Epididymides
Esophagus
Eyes
Femur with bone marrow
Gross lesions
*Heart
Ileum
Jejunum
*Kidneys (including proximal tubules of the cortex)
Lacrimal gland (exorbital)
*Liver
*Lung/Bronchi
Lymph node (mesenteric)
Mammary gland
*Ovaries
Pancreas
Pituitary
Prostate
Rectum
Salivary gland (submandibular)
Sciatic nerve
Seminal vesicles
Skeletal muscle (thigh)
Skin (exposure and non-exposure areas)
Spinal cord (cervical, mid-thoracic and lumbar)
*Spleen
Sternum with bone marrow
Stomach
*Testes
Thymus
Thyroid gland with parathyroids
Trachea
Urinary bladder
Uterus
Vagina

*Weighed at scheduled necropsy. Paired organs were weighed as a unit.

All tissues and organs collected at necropsy were examined microscopically in all control and high dose animals. Because an apparent test article-related lesion was observed in the skin (exposure site) of high dose animals, this tissue and potential target organs of aminoglycosides identified in the protocol (kidneys, ears and sciatic nerve) were histologically evaluated in low and mid dose animals.

3.5 Statistical Analyses

For each sex, Analysis of Variance tests was conducted on body weight, food consumption, hematology, clinical chemistry and organ weight data. Organ weight analysis considered weights relative to brain weight. If a significant F ratio was obtained from an ANOVA test ($p \leq 0.05$), Dunnett's t test was used for pair-wise comparisons with the control group.

Quantitative data were tabulated and are presented in the report. In addition to the written report, individual data in "ASCII" form and summary data tables of parameters and variability were transmitted to the Sponsor on magnetic media (computer diskette). The transcribed data on disk are no longer considered GLP compliant.

4. RESULTS

4.1 Mortality and Clinical Signs

Summaries of clinical signs are presented in Tables 2.1 and 2.2. Individual clinical signs are contained in Appendix 2.

Clinical signs of toxicity were not observed during the study, except for dermal irritation at the site of treatment (subsequently discussed). No treatment-related deaths occurred, but one low dose male (animal no. 330) accidently died on day 23. This animal had become extremely intolerant of the restraining jacket (biting, struggling, vocalizing, etc.). On day 23, after being placed in its jacket, the animal freed itself from physical restraint, jumped off the table and landed on the floor. Although it appeared to survive, it convulsed and stopped breathing after it was returned to its cage. Gross necropsy findings of this animal were non-remarkable and no test article-related changes were seen in the kidney, exposure area skin, sciatic nerve and ears.

4.2 Dermal Irritation Evaluations

Weekly dermal irritation evaluation (Draize scores) of the treatment sites is presented in Tables 3.1 and 3.2. Representative photographs demonstrating dermal irritation on day 6 are shown in Appendix 10.

On day 4, the twice daily dermal application of the test article resulted in well-defined erythema (draize score of 2) at the exposure site in some mid and high dose animals, and very slight erythema was seen in a few low dose animals. On day 5, moderate to severe erythema (draize score of 3) was seen in the mid and high dose groups. Several low dose animals had well defined erythema. On day 6 (prior to treatment), photographs were taken of the treatment sites in representative animals exhibiting the above-described dermal irritation (Appendix 10). The size of the affected area appeared to correspond to the volume of test article cream applied to the back, however the severity of dermal irritation was not volume dependent. Dermal irritation severity was generally similar in high dose and mid dose animals. Low dose animals had less dermal irritation apparently

because of the very small volume of test article applied. On days 4 and 5, control animals did not exhibit any dermal irritation, and edema formation has not been observed in any animal.

On day 7, after the reduction of WR279396 administration to once daily on day 6, dermal irritation severity greatly diminished from that seen in test article-treated animals on days 4 and 5. Dermal irritation was limited to very slight erythema in mid and high dose animals, except for one high dose male (no. 370) which had well-defined erythema at its exposure site. At that time, several low dose animals also had very slight erythema. On day 14, very slight erythema was observed in all high dose males and most high dose females. Dermal irritation in mid dose animals on day 14 appeared to be a residual effect from the twice daily treatment. At that time, dermal irritation was not observed in low dose animals. By day 21, dermal irritation was limited to the high dose animals, except for a mid dose male and female, and consisted of very slight erythema. On day 27, following three weeks of daily dermal application of WR279396, dermal irritation was generally limited to high dose animals and consisted of very slight erythema (barely perceptible) without edema formation. Very slight erythema was observed in one low dose female and one mid dose male on day 27. The sporadic observation of erythema in these two animals may reflect a greater localization of the test article, *i.e.* greater amount in a small area. Edema formation was not observed during the study.

4.3 Body Weights

Summaries of body weights and summaries of weight gains are presented in Tables 4.1 - 4.2 and 5.1 - 5.2, respectively. Individual body weights and weight gains are contained in Appendix 3. In addition, summaries of body weights are graphically depicted in Figures 1 (males) and 2 (females).

Body weights were not affected by WR279396 treatment.

4.4 Food Consumption

Summaries of food consumption are presented in Table 6.1 and 6.2. Individual food consumption data are shown in Appendix 4.

Food consumption was not affected by test article treatment. During the last week of treatment, high dose males had a statistically significant increase in mean daily food consumption. This slight increase in food intake was not considered biologically significant.

4.5 Clinical Pathology

Summaries of clinical chemistry tests are presented in Table 7.1 - 7.2. Individual clinical chemistry data are presented in Appendix 5. Summaries of hematological tests are presented in Table 8.1 - 8.2. Individual hematology data are shown in Appendix 6.

Clinical chemistry parameters were not affected by test article treatment. Since neither BUN nor creatinine levels were altered by treatment, overt nephrotoxicity was not apparent. A slight, but statistically significant increase in serum albumin observed in mid dose females on day 28 was not considered biologically significant. At that time, increases in serum albumin levels were not seen in high dose animals or in mid dose males.

Hematology parameters were not affected by WR279396 treatment.

4.6 Ophthalmology

The Ophthalmology Report is contained in Appendix 7. WR279396 treatment did not result in treatment-related ophthalmic lesions.

4.7 Organ Weights

Organ weight summaries expressed as % brain weight are presented in Table 9.1 - 9.2. Individual organ weight data are contained in Appendix 8.

Organ weights (% brain weight) were not affected by test article treatment. The increase in relative lung weight in mid dose males, but not in high dose animals, was not considered biologically significant. It was apparently due to a slight increase in the absolute lung weights of two mid dose males. This may be an artifact secondary to whole body perfusion.

4.8 Pathology

The Pathology Report is contained in Appendix 9. The summary of gross and microscopic lesions is shown in Table 10.

The dermal administration of WR279396 was associated with microscopic changes in the skin exposure area. Acanthosis, consisting of the focal thickening of the epidermis due to a thicker than normal stratum spinosum layer, was observed in 3 of 10 high dose males (mean group severity = 0.30, maximum score = 4.00), 4 of 10 high dose females (mean group severity = 0.50), 1 of 10 mid dose males (mean group severity = 0.10), and 1 of 10 control females (mean group severity = 0.10). These epidermal changes were not observed in mid dose females, low dose animals or control males. Therefore, the minimal to mild acanthosis was considered a test article-related change.

No other histologic changes were considered to be related to WR279396 treatment. Treatment-related changes were not observed in the ears, kidneys or sciatic nerve. Hyperkeratosis was observed more frequently at the skin exposure area than the non-exposure area. This change was characterized by multiple layers of retained keratinized epithelial cells. However, because this dermal change was observed in a similar

frequency in animals treated with the WR279396 vehicle and the high dose of WR279396, it was considered to be a response to the vehicle and/or a response to rubbing during the application and/or removal of the control or test article cream.

5. DISCUSSION/CONCLUSION

This study evaluated the toxicity of WR279396 in CD® rats following four weeks of daily dermal application. The results are summarized in Table 1. Dermal application of 1.67 ml/kg/day of WR279396 induced localized, minimal dermal toxicity at the exposure site in high dose animals (500 mg/kg/day of paromomycin + 16.7 mg/kg/day of gentamicin). After four weeks of treatment, very slight erythema (draize score = 1, barely perceptible), not accompanied by edema formation, was seen in most high dose animals. Dermal irritation in mid and low dose animals on days 7 and 14 were considered residual effects of the twice daily treatment on days 0 - 5. Acanthosis, thickening of the stratum spinosum layer of the epidermis, was seen in several high dose animals and was generally of minimal severity in affected animals. Except for one mid dose male, these dermal changes were not seen at lower dosing volumes of WR279396, *i.e.* 0.07 or 0.33 ml/kg/day (doses of 20 and 100 mg/kg/day of paromomycin + 0.7 and 3.3 mg/kg/day of gentamicin, respectively). Clinical signs, body weights, food intake, clinical chemistry and hematology parameters, ophthalmic evaluations and organ weights were not affected by test article treatment in any of the dose levels tested.

The test article was administered at a constant test article concentration, and the dosing volume of cream was varied. Therefore, if the cream was uniformly spread in a thin monolayer in all treatment groups, one might expect that the size of the affected area may vary, but not the severity of the dermal irritation. However, because the dosing volume of the high dose group was considerably larger compared to that in lower dose groups, the cream was apparently, but unavoidably spread thicker on the backs of high dose animals, especially in centralized areas where dermal irritation was generally observed. Therefore, the localized dermal observed following the once daily application of WR279396 in high dose animals was due to a greater amount of the test article per unit area compared to lower dose groups. Very slight erythema in one mid and low dose animal on day 27 may indicate an uneven application of the test article, producing a greater amount of test article per unit area.

Prior to the reduction in the frequency of dermal applications, dermal irritation was more severe, *i.e.* moderate to severe erythema (draize score = 3). On days 0 - 5, the test and control articles were applied twice, approximately 3 - 4 hours apart, *i.e.* the doses were twice that which were administered on day 6 and thereafter. However, the increased severity in the dermal irritation observed on day 5 (moderate to severe erythema) could not be accounted solely on the basis of increased dose levels of paromomycin and gentamicin. The severity of the dermal irritation significantly and rapidly diminished in all test article-treated groups following the reduction in the frequency of treatment from twice to once daily. By day 21, dermal irritation was generally not observed in mid and low dose animals. Second, high dose animals were still receiving greater amounts of test article on days 6 through the remainder of the study (1.67 ml/kg/day) compared with either mid dose animals (0.33 ml/kg/day x 2) or low dose animals (0.07 ml/kg/day x 2). At these lower total doses of WR279396 per day, greater localized dermal irritation was still observed

in mid dose and low dose animals (moderate to severe erythema and well-defined erythema) compared to that seen in the "new" high dose (very slight erythema). Therefore, the duration of exposure and/or the frequency of test article application (rubbing on and/or removal of the material) appears to significantly affect the localized irritation produced by paromomycin + gentamicin in the Iowa 232 formulation.

In summary, following the single daily dermal administration of WR279396, test article-induced toxicity was limited to minimal dermal toxicity at the treatment site in high dose animals (1.67 ml/kg/day WR279396). No other test article-related changes were observed. A no-observed effect level (NOEL) was considered to be at or near 0.33 ml/kg/day of WR279396 administered once daily, corresponding to 50 mg/kg/day paromomycin + 3.3 mg/kg/day gentamicin in Iowa Formulation 232. However, more frequent application of test article per day results in dermal irritation and potentially histologic changes in the skin at the exposure site. Following six days of treatment, the twice daily application of the volume of test article produced well-defined erythema in low dose animals and moderate to severe erythema in mid and high dose animals.

6. PERSONNEL

Study Director	Barry S. Levine, D.Sc., D.A.B.T.
Toxicologist	Clyde W. Wheeler, Ph.D.
Pathologist	Robert L. Morrissey, D.V.M., Ph.D., D.A.C.V.P.
Clinical Veterinarian	James E. Artwohl, D.V.M., M.S., D.A.C.L.A.M.
Veterinarian Support	Documented in the raw data
Ophthalmologist	Samuel J. Vainisi, D.V.M., D.A.C.V.O.
Clinical Laboratory	Maria Lang, A.H.T., C.V.T.
Tox. Lab Supervisor	Soudabeh Soura, B.S.
Lead Technician	Nancy Dinger, B.S.
Quality Assurance	Ronald C. Schoenbeck

Report preparation was assisted by Dr. Clyde Wheeler, Ms. Soudabeh Soura and Mr. Mukesh Pitroda.

7. ARCHIVES

The raw data, specimens, test article reserves, and final report are archived at the Toxicology Research Laboratory (TRL), University of Illinois at Chicago (UIC), Department of Pharmacology, 1940 W. Taylor St., Chicago, IL 60612-7353.

8. REFERENCE

Draize, J.H. (1965). Appraisal of the Safety of Chemicals in Foods, Drugs, and Cosmetics; Association of Food and Drug Officials of the U.S., (Austin, TX).

Table 1

FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD® RATS

Summary of Toxic Responses

Treatment	Vehicle (1.67 ml/kg/day)[a]	WR279396 (0.07 ml/kg/day)[a]	WR279396 (0.33 ml/kg/day)[a]	WR279396 (1.67 ml/kg/day)[a]
Rats/Sex	10	NE	10	10
Deaths[b]	-	1 (M-AC)	0	0
Clinical Signs	-	NE	NE	NE
Dermal Irritation Evaluations[c]	E/E 0M/0F E 0M/0F	E/E 0M/1F E 0M/0F	E/E 1M/0F E 0M/0F	E/E 7M/8F E 0M/0F
Body Weights/Gains	-	NE	NE	NE
Food Consumption	-	NE	NE	NE
Clinical Chemistry	-	NE	NE	NE
Hematology	-	NE	NE	NE
Ophthalmology	-	NE	NE	NE
Organ Weights	-	NE	NE	NE
Histopathology	Skin (exposure area) Acanthosis (1F)	NE	Skin (exposure area) Acanthosis (1M)	Skin (exposure area) Acanthosis (3M/4F)

CONCLUSIONS
Following the single daily dermal administration of WR279396, test article-induced toxicity was limited to minimal dermal toxicity at the treatment site in high dose animals (1.67 ml/kg/day WR279396). This included acanthosis, thickening of the stratum spinosum layer of the epidermis, and barely perceptible erythema. No other test article-related changes were observed. A no-observed effect level (NOEL) was considered to be at or near 0.33 ml/kg/day of WR279396 administered once daily, corresponding to 50 mg/kg/day paromomycin + 3.3 mg/kg/day gentamicin in Iowa Formulation 232. However, more frequent application of test article per day results in dermal irritation and potentially histologic changes in the skin at the exposure site. Following six days of treatment, the twice daily application of the volume of test article produced well-defined erythema in low dose animals and moderate to severe erythema in mid and high dose animals.

[a]On days 0 - 5, animals received twice the volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

[b]AC = accidental death

[c]Dermal evaluations on day 27
E/E = Erythema and Eschar formation
E = edema

NE = No effect

M = Male, F = Female

Table 2.1

FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD® RATS

SUMMARY OF CLINICAL SIGNS

STUDY: 176 SEX: MALE

GROUP:	1-M	2-M	3-M	4-M
Accidental Death	0	1	0	0
Scheduled Sacrifice	10	9	10	10
Normal 1st Sign	10	10	10	10
Normal 2nd Sign	10	10	10	10
Total Number of Animals	10	10	10	10

Group 1-M: VEHICLE (1.67 ml/kg/day)**
Group 2-M: WR279396 (0.07 ml/kg/day)**
Group 3-M: WR279396 (0.33 ml/kg/day)**
Group 4-M: WR279396 (1.67 ml/kg/day)**

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

Table 2.2

FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD® RATS

SUMMARY OF CLINICAL SIGNS

STUDY: 176 SEX: FEMALE

GROUP:	1-F	2-F	3-F	4-F
Scheduled Sacrifice	10	10	10	10
Normal 1st Sign	10	10	10	10
Normal 2nd Sign	10	10	10	10
Total Number of Animals	10	10	10	10

Group 1-F: VEHICLE (1.67 ml/kg/day)**
Group 2-F: WR279396 (0.07 ml/kg/day)**
Group 3-F: WR279396 (0.33 ml/kg/day)**
Group 4-F: WR279396 (1.67 ml/kg/day)**

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

Table 3.1

FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD® RATS

Dermal Irritation Evaluation (Males)

		Day 0[a]		Day 7[a]		Day 14[a]		Day 21[a]		Day 27[a]	
	Animal No.	E/E	E	E/E	E	E/E	E	E/E	E	E/E	E
Treatment Group 1 Vehicle 1.67 ml/kg/day[b]	301	0	0	0	0	0	0	0	0	0	0
	302	0	0	0	0	0	0	0	0	0	0
	303	0	0	0	0	0	0	0	0	0	0
	304	0	0	0	0	0	0	0	0	0	0
	305	0	0	0	0	0	0	0	0	0	0
	306	0	0	0	0	0	0	0	0	0	0
	307	0	0	0	0	0	0	0	0	0	0
	308	0	0	0	0	0	0	0	0	0	0
	309	0	0	0	0	0	0	0	0	0	0
	310	0	0	0	0	0	0	0	0	0	0
Treatment Group 2 WR279396 0.07 ml/kg/day[b]	321	0	0	0	0	0	0	0	0	0	0
	322	0	0	0	0	0	0	0	0	0	0
	323	0	0	1	0	0	0	0	0	0	0
	324	0	0	0	0	0	0	0	0	0	0
	325	0	0	0	0	0	0	0	0	0	0
	326	0	0	1	0	0	0	0	0	0	0
	327	0	0	0	0	0	0	0	0	0	0
	328	0	0	0	0	0	0	0	0	0	0
	329	0	0	0	0	0	0	0	0	0	0
	330	0	0	0	0	0	0	0	0	c	c

[a]Prior to treatment
[b]On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days , the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.
[c]Accidental death on day 23.

E/E = Erythema and Eschar formation:
0 = No erythema
1 = Very slight erythema (barely perceptible)
2 = Well defined erythema
3 = Moderate to severe erythema
4 = Severe erythema (beet redness) to slight eschar formation (injuries to depth)

E = Edema formation:
0 = No edema
1 = Very slight edema (barely perceptible)
2 = Slight edema (edges of area well defined by definite raising)
3 = Moderate edema (raised approximately 1.0 mm)
4 = Severe edema (raised more than 1.0 mm and extending beyond the area of exposure)

Table 3.1 (contd.)

FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD® RATS

Dermal Irritation Evaluation (Males)

		Day 0[a]		Day 7[a]		Day 14[a]		Day 21[a]		Day 27[a]	
	Animal No.	E/E	E	E/E	E	E/E	E	E/E	E	E/E	E
Treatment Group 3 WR279396 0.33 ml/kg/day[b]	341	0	0	1	0	1	0	0	0	0	0
	342	0	0	1	0	1	0	0	0	0	0
	343	0	0	1	0	1	0	0	0	0	0
	344	0	0	1	0	1	0	0	0	1	0
	345	0	0	1	0	0	0	0	0	0	0
	346	0	0	1	0	1	0	1	0	0	0
	347	0	0	1	0	0	0	0	0	0	0
	348	0	0	0	0	1	0	0	0	0	0
	349	0	0	1	0	1	0	0	0	0	0
	350	0	0	1	0	0	0	0	0	0	0
Treatment Group 4 WR279396 1.67 ml/kg/day[b]	361	0	0	1	0	1	0	0	0	0	0
	362	0	0	1	0	1	0	1	0	1	0
	363	0	0	1	0	1	0	1	0	1	0
	364	0	0	1	0	1	0	1	0	1	0
	365	0	0	1	0	1	0	1	0	1	0
	366	0	0	1	0	1	0	0	0	1	0
	367	0	0	1	0	1	0	1	0	1	0
	368	0	0	1	0	1	0	1	0	0	0
	369	0	0	1	0	1	0	0	0	0	0
	370	0	0	2	0	1	0	1	0	1	0

[a]Prior to treatment
[b]On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days , the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.
[c]Accidental death on day 23.

E/E = Erythema and Eschar formation:
0 = No erythema
1 = Very slight erythema (barely perceptible)
2 = Well defined erythema
3 = Moderate to severe erythema
4 = Severe erythema (beet redness) to slight eschar formation (injuries to depth)

E = Edema formation:
0 = No edema
1 = Very slight edema (barely perceptible)
2 = Slight edema (edges of area well defined by definite raising)
3 = Moderate edema (raised approximately 1.0 mm)
4 = Severe edema (raised more than 1.0 mm and extending beyond the area of exposure)

Table 3.2

FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD® RATS

Dermal Irritation Evaluation (Females)

		Day 0[a]		Day 7[a]		Day 14[a]		Day 21[a]		Day 27[a]	
	Animal No.	E/E	E	E/E	E	E/E	E	E/E	E	E/E	E
Treatment Group 1 Vehicle 1.67 ml/kg/day[b]	311	0	0	0	0	0	0	0	0	0	0
	312	0	0	0	0	0	0	0	0	0	0
	318	0	0	0	0	0	0	0	0	0	0
	314	0	0	0	0	0	0	0	0	0	0
	315	0	0	0	0	0	0	0	0	0	0
	336	0	0	0	0	0	0	0	0	0	0
	314	0	0	0	0	0	0	0	0	0	0
	318	0	0	0	0	0	0	0	0	0	0
	318	0	0	0	0	0	0	0	0	0	0
	320	0	0	0	0	0	0	0	0	0	0
Treatment Group 2 WR279396 0.07 ml/kg/day[b]	331	0	0	0	0	0	0	0	0	1	0
	332	0	0	0	0	0	0	0	0	0	0
	333	0	0	1	0	0	0	0	0	0	0
	334	0	0	0	0	0	0	0	0	0	0
	335	0	0	0	0	0	0	0	0	0	0
	336	0	0	0	0	0	0	0	0	0	0
	337	0	0	0	0	0	0	0	0	0	0
	338	0	0	1	0	0	0	0	0	0	0
	339	0	0	1	0	0	0	0	0	0	0
	340	0	0	1	0	0	0	0	0	0	0

[a]Prior to treatment
[b]On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days , the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

E/E = Erythema and Eschar formation:
0 = No erythema
1 = Very slight erythema (barely perceptible)
2 = Well defined erythema
3 = Moderate to severe erythema
4 = Severe erythema (beet redness) to slight eschar formation (injuries to depth)

E = Edema formation:
0 = No edema
1 = Very slight edema (barely perceptible)
2 = Slight edema (edges of area well defined by definite raising)
3 = Moderate edema (raised approximately 1.0 mm)
4 = Severe edema (raised more than 1.0 mm and extending beyond the area of exposure)

Table 3.2 (contd.)

FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD® RATS

Dermal Irritation Evaluation (Females)

		Day 0[a]		Day 7[a]		Day 14[a]		Day 21[a]		Day 27[a]	
	Animal No.	E/E	E	E/E	E	E/E	E	E/E	E	E/E	E
Treatment Group 3 WR279396 0.33 ml/kg/day[b]	351	0	0	1	0	1	0	0	0	0	0
	357	0	0	1	0	1	0	1	0	0	0
	353	0	0	0	0	0	0	0	0	0	0
	355	0	0	1	0	0	0	0	0	0	0
	355	0	0	1	0	0	0	0	0	0	0
	356	0	0	1	0	1	0	0	0	0	0
	357	0	0	1	0	0	0	0	0	0	0
	357	0	0	1	0	0	0	0	0	0	0
	358	0	0	0	0	0	0	0	0	0	0
	360	0	0	1	0	0	0	0	0	0	0
Treatment Group 4 WR279396 1.67 ml/kg/day[b]	371	0	0	1	0	0	0	1	0	1	0
	372	0	0	1	0	0	0	1	0	1	0
	374	0	0	1	0	0	0	1	0	1	0
	374	0	0	1	0	1	0	1	0	1	0
	375	0	0	1	0	1	0	1	0	0	0
	376	0	0	1	0	1	0	1	0	1	0
	377	0	0	1	0	1	0	1	0	1	0
	378	0	0	1	0	1	0	1	0	1	0
	379	0	0	1	0	1	0	1	0	0	0
	380	0	0	1	0	1	0	1	0	1	0

[a]Prior to treatment
[b]On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days , the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

E/E = Erythema and Eschar formation:
0 = No erythema
1 = Very slight erythema (barely perceptible)
2 = Well defined erythema
3 = Moderate to severe erythema
4 = Severe erythema (beet redness) to slight eschar formation (injuries to depth)

E = Edema formation:
0 = No edema
1 = Very slight edema (barely perceptible)
2 = Slight edema (edges of area well defined by definite raising)
3 = Moderate edema (raised approximately 1.0 mm)
4 = Severe edema (raised more than 1.0 mm and extending beyond the area of exposure)

Table 4.1

FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD® RATS

SUMMARY OF BODY WEIGHTS (Grams)

STUDY: 176 SEX: MALE

PERIOD	GROUP:	1-M	2-M	3-M	4-M
DAY -3	MEAN	248	248	248	248
	S.D.	6.5	6.3	7.6	6.4
	N	10	10	10	10
DAY 0	MEAN	273	270	271	269
	S.D.	6.4	7.8	9.3	4.8
	N	10	10	10	10
DAY 7	MEAN	325	321	325	321
	S.D.	9.4	13.5	14.1	12.2
	N	10	10	10	10
DAY 14	MEAN	363	361	368	365
	S.D.	14.2	17.4	20.8	21.4
	N	10	10	10	10
DAY 21	MEAN	393	399	407	399
	S.D.	17.5	20.4	26.9	27.5
	N	10	10	10	10
DAY 27	MEAN	418	425	439	431
	S.D.	23.9	19.5	29.9	29.1
	N	10	9	10	10

Analysis of Variance using DUNNETT'S Procedure

Group 1-M: VEHICLE (1.67 ml/kg/day)**
Group 2-M: WR279396 (0.07 ml/kg/day)**
Group 3-M: WR279396 (0.33 ml/kg/day)**
Group 4-M: WR279396 (1.67 ml/kg/day)**

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

Table 4.2

FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD® RATS

SUMMARY OF BODY WEIGHTS (Grams)

STUDY: 176 SEX: FEMALE

PERIOD	GROUP:	1-F	2-F	3-F	4-F
DAY -3	MEAN	191	191	191	191
	S.D.	9.7	9.4	8.5	9.5
	N	10	10	10	10
DAY 0	MEAN	198	200	198	200
	S.D.	8.3	12.1	7.9	8.8
	N	10	10	10	10
DAY 7	MEAN	223	229	223	228
	S.D.	9.8	14.0	12.9	11.9
	N	10	10	10	10
DAY 14	MEAN	247	255	245	255
	S.D.	13.0	19.2	23.0	13.8
	N	10	10	10	10
DAY 21	MEAN	265	276	262	270
	S.D.	13.3	21.1	26.1	19.8
	N	10	10	10	10
DAY 27	MEAN	279	289	269	279
	S.D.	13.5	20.0	26.5	26.0
	N	10	10	10	10

Analysis of Variance using DUNNETT'S Procedure

Group 1-F: VEHICLE (1.67 ml/kg/day)**
Group 2-F: WR279396 (0.07 ml/kg/day)**
Group 3-F: WR279396 (0.33 ml/kg/day)**
Group 4-F: WR279396 (1.67 ml/kg/day)**

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

Table 5.1

FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD® RATS

SUMMARY OF WEIGHT GAINS (Grams)

STUDY: 176 SEX: MALE

PERIOD[a]	DOSE: (mg/kg) GROUP:	1-M	2-M	3-M	4-M
DAY 7[b]	MEAN	52	51	54	51
	S.D.	5.5	7.6	7.6	11.6
	N	10	10	10	10
DAY 14	MEAN	38	39	44	44
	S.D.	7.5	6.5	8.3	10.2
	N	10	10	10	10
DAY 21	MEAN	30	38	38	34
	S.D.	9.5	5.4	7.3	8.0
	N	10	10	10	10
DAY 27	MEAN	25	30	32	32
	S.D.	7.7	2.9	8.0	5.9
	N	10	9	10	10
TOTAL GAIN	MEAN	145	156	168	162
	S.D.	22.8	15.8	25.2	28.1
	N	10	9	10	10

Analysis of Variance using DUNNETT'S Procedure

[a] Successive periods

[b] Baseline is day 0

Group 1-M: VEHICLE (1.67 ml/kg/day)**
Group 2-M: WR279396 (0.07 ml/kg/day)**
Group 3-M: WR279396 (0.33 ml/kg/day)**
Group 4-M: WR279396 (1.67 ml/kg/day)**

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

Table 5.2

FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD® RATS

SUMMARY OF WEIGHT GAINS (Grams)

STUDY: 176 SEX: FEMALE

PERIOD[a]	DOSE: (mg/kg) GROUP:	1-F	2-F	3-F	4-F
DAY 7[b]	MEAN	24	28	25	28
	S.D.	5.1	5.6	7.7	9.5
	N	10	10	10	10
DAY 14	MEAN	25	26	22	27
	S.D.	9.6	7.2	11.3	4.9
	N	10	10	10	10
DAY 21	MEAN	17	21	17	15
	S.D.	4.4	6.8	6.3	7.4
	N	10	10	10	10
DAY 27	MEAN	15	13	8	10
	S.D.	5.5	8.6	5.7	7.6
	N	10	10	10	10
TOTAL GAIN	MEAN	81	89	71	80
	S.D.	14.1	12.3	22.3	23.3
	N	10	10	10	10

Analysis of Variance using DUNNETT'S Procedure

[a]Successive periods

[b]Baseline is day 0

Group 1-F: VEHICLE (1.67 ml/kg/day)**
Group 2-F: WR279396 (0.07 ml/kg/day)**
Group 3-F: WR279396 (0.33 ml/kg/day)**
Group 4-F: WR279396 (1.67 ml/kg/day)**

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

Table 6.1

FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD® RATS

SUMMARY OF DAILY MEAN FOOD CONSUMPTION (Grams)

STUDY: 176 SEX: MALE

PERIOD[a]	GROUP:	1-M	2-M	3-M	4-M
DAY 0[b]	INTAKE (g)	23.4	22.8	22.7	23.0
	S.D.	0.96	0.94	1.58	1.38
	N	10	10	10	10
DAY 7	INTAKE (g)	26.6	26.6	26.1	26.7
	S.D.	1.05	1.70	1.36	1.63
	N	10	10	9	10
DAY 14	INTAKE (g)	26.3	25.9	26.3	27.9
	S.D.	1.46	1.86	2.16	2.50
	N	10	10	10	10
DAY 21	INTAKE (g)	25.5	25.7	26.7	27.2
	S.D.	1.57	1.76	2.33	2.51
	N	10	10	10	10
DAY 27	INTAKE (g)	25.2	26.6	27.6	30.4*
	S.D.	5.04	1.70	2.27	2.31
	N	10	9	10	10

* P less than .05 Analysis of Variance using DUNNETT'S Procedure

[a]Inclusive intervals

[b]Food in on day -6

Group 1-M: VEHICLE (1.67 ml/kg/day)**
Group 2-M: WR279396 (0.07 ml/kg/day)**
Group 3-M: WR279396 (0.33 ml/kg/day)**
Group 4-M: WR279396 (1.67 ml/kg/day)**

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

Table 6.2

FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD® RATS

SUMMARY OF DAILY MEAN FOOD CONSUMPTION (Grams)

STUDY: 176 SEX: FEMALE

PERIOD[a]	GROUP:	1-F	2-F	3-F	4-F
DAY 0[b]	INTAKE (g)	17.1	17.3	16.9	17.0
	S.D.	1.22	1.40	1.70	1.21
	N	10	10	10	10
DAY 7	INTAKE (g)	20.8	20.4	19.1	20.0
	S.D.	1.72	1.39	1.60	1.63
	N	10	10	10	10
DAY 14	INTAKE (g)	20.8	20.9	20.3	21.4
	S.D.	1.15	1.74	2.86	1.66
	N	10	10	10	10
DAY 21	INTAKE (g)	20.1	21.0	19.9	20.0
	S.D.	1.27	1.67	3.29	2.40
	N	10	10	10	10
DAY 27	INTAKE (g)	23.2	22.5	20.8	22.9
	S.D.	3.60	2.86	3.09	4.58
	N	10	10	10	10

Analysis of Variance using DUNNETT'S Procedure

[a] Inclusive intervals

[b] Food in on day -6

Group 1-F: VEHICLE (1.67 ml/kg/day)**
Group 2-F: WR279396 (0.07 ml/kg/day)**
Group 3-F: WR279396 (0.33 ml/kg/day)**
Group 4-F: WR279396 (1.67 ml/kg/day)**

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

Table 7.1

FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD® RATS

SUMMARY OF CLINICAL CHEMISTRY TESTS
PERIOD: DAY27/28

STUDY ID: UIC-12A
STUDY NO: 176

SEX: MALE

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

TEST(s):	ALT	SDH	TP	ALB	GLOB	TBA	ALKP	CHOL
UNITS:	IU/L	IU/L	g/dL	g/dL	g/dL	umol/L	IU/L	mg/dL
Group: 1-M : VEHICLE (1.67 ml/kg/day)**								
MEAN	68	13.4	7.4	4.0	3.4	42.8	420	65
SD	20.3	3.52	0.33	0.20	0.32	19.89	100.3	12.9
N	10	10	10	10	10	10	10	10
Group: 2-M : WR279396 (0.07 ml/kg/day)**								
MEAN	56	12.1	7.5	4.0	3.5	40.4	371	72
SD	7.7	6.02	0.36	0.27	0.35	23.37	99.4	7.7
N	9	9	9	9	9	9	9	9
Group: 3-M : WR279396 (0.33 ml/kg/day)**								
MEAN	58	10.4	7.6	4.0	3.5	28.4	387	67
SD	9.9	3.69	0.35	0.26	0.23	15.07	92.1	7.1
N	10	10	10	10	10	10	10	10
Group: 4-M : WR279396 (1.67 ml/kg/day)**								
MEAN	62	9.9	7.4	4.0	3.4	30.3	369	75
SD	19.3	4.82	0.44	0.28	0.35	18.03	57.9	7.7
N	10	10	10	10	10	10	10	10

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD® RATS

SUMMARY OF CLINICAL CHEMISTRY TESTS
PERIOD: DAY27/28

STUDY ID: UIC-12A
STUDY NO: 176

SEX: MALE

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

TEST(s):	BUN	CREAT	NA	K	CL	CA	IP	GLU
UNITS:	mg/dL	mg/dL	mEq/L	mEq/L	mEq/L	mg/dL	mg/dL	mg/dL
Group: 1-M : VEHICLE (1.67 ml/kg/day)**								
MEAN	16.3	0.55	144	5.67	108	10.7	9.7	155
SD	1.88	0.047	1.5	0.542	3.2	0.56	0.93	26.3
N	10	10	10	10	10	10	10	10
Group: 2-M : WR279396 (0.07 ml/kg/day)**								
MEAN	16.4	0.53	144	5.94	106	10.8	9.3	161
SD	3.29	0.048	1.1	0.827	5.7	0.52	1.08	35.1
N	9	9	9	9	9	9	9	9
Group: 3-M : WR279396 (0.33 ml/kg/day)**								
MEAN	16.5	0.55	144	5.67	106	10.9	9.6	158
SD	1.97	0.060	1.1	0.598	3.5	0.45	0.79	34.2
N	10	10	10	10	10	10	10	10
Group: 4-M : WR279396 (1.67 ml/kg/day)**								
MEAN	18.5	0.54	145	5.80	106	11.1	9.8	173
SD	2.49	0.058	2.4	1.003	4.9	0.89	1.09	41.4
N	10	10	10	10	10	10	10	10

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

Table 7.2

FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD® RATS

SUMMARY OF CLINICAL CHEMISTRY TESTS
PERIOD: DAY27/28

STUDY ID: UIC-12A
STUDY NO: 176

SEX: FEMALE

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

TEST(s):	ALT	SDH	TP	ALB	GLOB	TBA	ALKP	CHOL
UNITS:	IU/L	IU/L	g/dL	g/dL	g/dL	umol/L	IU/L	mg/dL
Group: 1-F : VEHICLE (1.67 ml/kg/day)**								
MEAN	58	12.6	7.6	4.2	3.5	25.5	234	66
SD	8.5	2.98	0.52	0.31	0.43	12.65	29.1	7.5
N	10	10	10	10	10	10	10	10
Group: 2-F : WR279396 (0.07 ml/kg/day)**								
MEAN	51	13.4	7.9	4.4	3.5	19.0	238	62
SD	8.8	4.35	0.54	0.24	0.56	4.39	108.7	9.2
N	10	10	10	10	10	10	10	10
Group: 3-F : WR279396 (0.33 ml/kg/day)**								
MEAN	58	16.6	8.0	4.6*	3.4	16.7	239	64
SD	12.7	3.59	0.48	0.29	0.23	2.59	76.4	8.6
N	10	10	10	10	10	10	10	10
Group: 4-F : WR279396 (1.67 ml/kg/day)**								
MEAN	56	9.9	7.9	4.4	3.6	21.4	289	72
SD	16.9	4.56	0.58	0.27	0.38	4.49	71.7	11.4
N	10	10	10	10	10	10	10	10

*-Significant Difference from Control P < .05

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD® RATS

SUMMARY OF CLINICAL CHEMISTRY TESTS
PERIOD: DAY27/28

STUDY ID: UIC-12A
STUDY NO: 176

SEX: FEMALE

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

TEST(s):	BUN	CREAT	NA	K	CL	CA	IP	GLU
UNITS:	mg/dL	mg/dL	mEq/L	mEq/L	mEq/L	mg/dL	mg/dL	mg/dL
Group: 1-F : VEHICLE (1.67 ml/kg/day)**								
MEAN	16.8	0.56	143	5.61	105	10.5	8.2	146
SD	2.52	0.045	2.0	0.476	3.3	0.54	0.79	17.1
N	10	10	10	10	10	10	10	10
Group: 2-F : WR279396 (0.07 ml/kg/day)**								
MEAN	17.1	0.53	143	5.63	109	10.6	8.8	163
SD	2.17	0.153	1.7	0.741	5.6	0.53	1.14	17.9
N	10	10	10	10	10	10	10	10
Group: 3-F : WR279396 (0.33 ml/kg/day)**								
MEAN	17.5	0.60	143	5.41	107	11.0	8.5	155
SD	1.94	0.072	1.8	0.443	3.8	0.59	1.18	35.6
N	10	10	10	10	10	10	10	10
Group: 4-F : WR279396 (1.67 ml/kg/day)**								
MEAN	16.0	0.55	144	5.58	105	10.8	7.9	153
SD	1.24	0.048	1.7	0.454	2.7	0.53	1.08	20.0
N	10	10	10	10	10	10	10	10

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

Table 8.1

FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD® RATS

SUMMARY OF HEMATOLOGICAL TESTS
PERIOD: DAY27/28

STUDY ID: UIC-12A
STUDY NO: 176

SEX: MALE

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

TEST(s):	RBC	HGB	HCT	MCV	MCH	MCHC	RETICS	NRBC
UNITS:	10^6/mm^3	g/dL	%	fL	pg	g/dL	% RBCs	COUNT
Group: 1-M : VEHICLE (1.67 ml/kg/day)**								
MEAN	7.60	15.8	43.1	56.7	20.8	36.7	0.1	0
SD	0.232	0.56	1.55	1.85	0.70	0.37	0.09	0.0
N	10	10	10	10	10	10	10	10
Group: 2-M : WR279396 (0.07 ml/kg/day)**								
MEAN	7.73	15.9	43.8	56.7	20.5	36.2	0.1	0
SD	0.238	0.50	1.47	2.02	0.69	0.30	0.14	0.0
N	9	9	9	9	9	9	9	9
Group: 3-M : WR279396 (0.33 ml/kg/day)**								
MEAN	7.57	15.8	43.9	58.0	21.0	36.1	0.1	0
SD	0.422	0.44	1.87	2.38	0.73	1.06	0.10	0.0
N	10	10	10	10	10	10	10	10
Group: 4-M : WR279396 (1.67 ml/kg/day)**								
MEAN	7.68	16.3	45.0	58.6	21.3	36.4	0.2	0
SD	0.420	0.74	2.09	2.75	1.08	0.40	0.15	0.0
N	10	10	10	10	10	10	10	10

WBC corrected for NRBC = or > 10

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

SUMMARY OF HEMATOLOGICAL TESTS
PERIOD: DAY27/28

STUDY ID: UIC-12A
STUDY NO: 176

SEX: MALE

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

TEST(s):	WBC	M. Neutrop	I. Neutrop	Lymphocyte	Monocytes	Eosinophil	Basophils	PLT
UNITS:	10^3/mm^3	10^3/mm^3	10^3/mm^3	10^3/mm^3	10^3/mm^3	10^3/mm^3	10^3/mm^3	10^3/mm^3
Group: 1-M : VEHICLE (1.67 ml/kg/day)**								
MEAN	17.4	1.9	0.0	14.9	0.4	0.1	0.0	978
SD	2.57	1.22	0.08	2.63	0.24	0.17	0.00	141.4
N	10	10	10	10	10	10	10	10
Group: 2-M : WR279396 (0.07 ml/kg/day)**								
MEAN	18.2	2.2	0.0	15.4	0.5	0.1	0.0	1045
SD	2.32	1.21	0.03	2.25	0.29	0.11	0.00	123.9
N	9	9	9	9	9	9	9	9
Group: 3-M : WR279396 (0.33 ml/kg/day)**								
MEAN	17.7	1.9	0.0	15.2	0.3	0.2	0.0	1006
SD	4.18	0.67	0.09	4.27	0.24	0.22	0.00	89.8
N	10	10	10	10	10	10	10	10
Group: 4-M : WR279396 (1.67 ml/kg/day)**								
MEAN	19.0	1.9	0.1	16.6	0.4	0.0	0.0	922
SD	5.91	1.79	0.08	5.91	0.18	0.06	0.00	92.9
N	10	10	10	10	10	10	10	10

WBC corrected for NRBC = or > 10

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

Table 8.2

FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD® RATS

SUMMARY OF HEMATOLOGICAL TESTS
PERIOD: DAY27/28

STUDY ID: UIC-12A
STUDY NO: 176

SEX: FEMALE

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

TEST(s):	RBC	HGB	HCT	MCV	MCH	MCHC	RETICS	NRBC
UNITS:	10^6/mm^3	g/dL	%	fL	pg	g/dL	% RBCs	COUNT
Group: 1-F : VEHICLE (1.67 ml/kg/day)**								
MEAN	7.17	15.4	41.5	57.9	21.5	37.1	0.2	0
SD	0.330	0.50	1.71	1.10	0.47	0.75	0.14	0.0
N	10	10	10	10	10	10	10	10
Group: 2-F : WR279396 (0.07 ml/kg/day)**								
MEAN	7.17	15.7	41.8	58.3	21.9	37.5	0.2	0
SD	0.455	1.05	2.56	1.61	0.56	0.54	0.24	0.0
N	10	10	10	10	10	10	10	10
Group: 3-F : WR279396 (0.33 ml/kg/day)**								
MEAN	7.22	15.6	41.6	57.7	21.6	37.4	0.2	0
SD	0.233	0.52	1.31	1.32	0.68	0.75	0.12	0.0
N	10	10	10	10	10	10	10	10
Group: 4-F : WR279396 (1.67 ml/kg/day)**								
MEAN	7.31	15.5	41.8	57.1	21.3	37.2	0.2	0
SD	0.532	0.85	2.76	1.12	0.60	0.75	0.14	0.0
N	10	10	10	10	10	10	10	10

WBC corrected for NRBC = or > 10

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD® RATS

SUMMARY OF HEMATOLOGICAL TESTS
PERIOD: DAY27/28

STUDY ID: UIC-12A
STUDY NO: 176
SEX: FEMALE

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

TEST(s):	WBC	M. Neutrop	I. Neutrop	Lymphocyte	Monocytes	Eosinophil	Basophils	PLT
UNITS:	10^3/mm^3	10^3/mm^3	10^3/mm^3	10^3/mm^3	10^3/mm^3	10^3/mm^3	10^3/mm^3	10^3/mm^3
Group: 1-F : VEHICLE (1.67 ml/kg/day)**								
MEAN	18.1	1.9	0.0	15.6	0.4	0.1	0.0	1115
SD	3.23	1.11	0.06	3.50	0.12	0.22	0.00	121.7
N	10	10	10	10	10	10	10	10
Group: 2-F : WR279396 (0.07 ml/kg/day)**								
MEAN	15.1	1.6	0.1	13.1	0.3	0.1	0.0	1018
SD	2.98	0.98	0.11	3.06	0.24	0.09	0.00	153.1
N	10	10	10	10	10	10	10	10
Group: 3-F : WR279396 (0.33 ml/kg/day)**								
MEAN	15.1	1.4	0.0	13.4	0.2	0.1	0.0	986
SD	2.48	0.72	0.00	2.34	0.20	0.14	0.00	130.3
N	10	10	10	10	10	10	10	10
Group: 4-F : WR279396 (1.67 ml/kg/day)**								
MEAN	16.0	1.2	0.0	14.5	0.3	0.1	0.0	1101
SD	5.77	0.81	0.09	5.11	0.25	0.11	0.00	94.3
N	10	10	10	10	10	10	10	10

WBC corrected for NRBC = or > 10

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

Table 9.1

FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD® RATS

ORGAN WEIGHT SUMMARY (% BRAIN WEIGHT)

STUDY: 176
SEX: MALE

ALL FATES DAYS: BEGINNING-29 ALL BALANCES
ANALYSIS OF VARIANCE USING DUNNETT'S PROCEDURE

GROUP:		1-M	2-M	3-M	4-M
Adrenal Glands(% BRAIN WEIGHT)					
	MEAN	4.09	3.50	3.60	3.93
	SD	1.036	0.631	1.284	0.679
	N	10	9	10	10
Heart(% BRAIN WEIGHT)					
	MEAN	64.69	64.66	70.96	65.76
	SD	11.098	6.787	9.562	7.842
	N	10	9	10	10
Kidneys(% BRAIN WEIGHT)					
	MEAN	167.04	181.04	178.74	172.86
	SD	19.892	16.523	24.644	27.576
	N	10	9	10	10
Liver(% BRAIN WEIGHT)					
	MEAN	806.73	774.09	824.03	812.25
	SD	92.081	85.503	95.493	115.787
	N	10	9	10	10
Lung/Bronchi(% BRAIN WEIGHT)					
	MEAN	101.76	107.67	120.37*	108.90
	SD	11.155	7.546	17.975	14.516
	N	10	9	10	10
Spleen(% BRAIN WEIGHT)					
	MEAN	36.04	38.66	36.57	40.35
	SD	5.548	5.093	4.965	8.458
	N	10	9	10	10
Testes(% BRAIN WEIGHT)					
	MEAN	150.15	149.54	148.59	157.13
	SD	12.141	15.200	8.561	18.426
	N	10	9	10	10

* - Significant difference P<.05

Group 1-M: VEHICLE (1.67 ml/kg/day)**
Group 2-M: WR279396 (0.07 ml/kg/day)**
Group 3-M: WR279396 (0.33 ml/kg/day)**
Group 4-M: WR279396 (1.67 ml/kg/day)**

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

Table 9.2

FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD® RATS

ORGAN WEIGHT SUMMARY (% BRAIN WEIGHT)

STUDY: 176
SEX: FEMALE

ALL FATES DAYS: BEGINNING-29 ALL BALANCES
ANALYSIS OF VARIANCE USING DUNNETT'S PROCEDURE

	GROUP:	1-F	2-F	3-F	4-F
Adrenal Glands(% BRAIN WEIGHT)					
	MEAN	4.23	4.70	5.05	4.73
	SD	1.194	0.518	1.122	0.985
	N	10	10	10	10
Heart(% BRAIN WEIGHT)					
	MEAN	47.98	52.12	47.81	50.04
	SD	8.199	7.105	7.213	9.551
	N	10	10	10	10
Kidneys(% BRAIN WEIGHT)					
	MEAN	121.20	133.75	130.69	131.38
	SD	20.993	19.295	20.715	15.131
	N	10	10	10	10
Liver(% BRAIN WEIGHT)					
	MEAN	551.26	577.64	568.98	567.17
	SD	76.569	57.425	87.072	66.034
	N	10	10	10	10
Lung/Bronchi(% BRAIN WEIGHT)					
	MEAN	92.96	89.20	91.95	92.05
	SD	24.027	12.738	13.181	7.696
	N	10	10	10	10
Ovaries(% BRAIN WEIGHT)					
	MEAN	8.60	9.29	8.34	8.01
	SD	3.682	3.887	3.222	1.947
	N	9	10	10	10
Spleen(% BRAIN WEIGHT)					
	MEAN	34.29	32.26	31.61	31.58
	SD	7.451	5.902	4.248	6.399
	N	10	10	10	10

Group 1-F: VEHICLE (1.67 ml/kg/day)**
Group 2-F: WR279396 (0.07 ml/kg/day)**
Group 3-F: WR279396 (0.33 ml/kg/day)**
Group 4-F: WR279396 (1.67 ml/kg/day)**

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

Table 10

FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD® RATS

Summary of Microscopic Lesions

MICROSCOPIC LESIONS[a,b]		Treatment			
ORGAN - lesion	Sex	Vehicle (1.67 ml/kg/day)[c]	WR279396 (0.07 ml/kg/day)[c]	WR279396 (0.33 ml/kg/day)[c]	WR279396 (1.67 ml/kg/day)[c]
SKIN (EXPOSURE AREA) - Acanthosis	M	0/10 (0.00)	0/10 (0.00)	1/10 (0.10)	3/10 (0.30)
	F	1/10 (0.10)	0/10 (0.00)	0/10 (0.00)	4/10 (0.50)

[a]Incidences (mean group severity) - Group mean severity was calculated by dividing the sum of all severity scores for a finding by the number of tissues examined.

[b]Lesion severity was scored as follows:

1 = Minimal 3 = Moderate
2 = Mild 4 = Marked

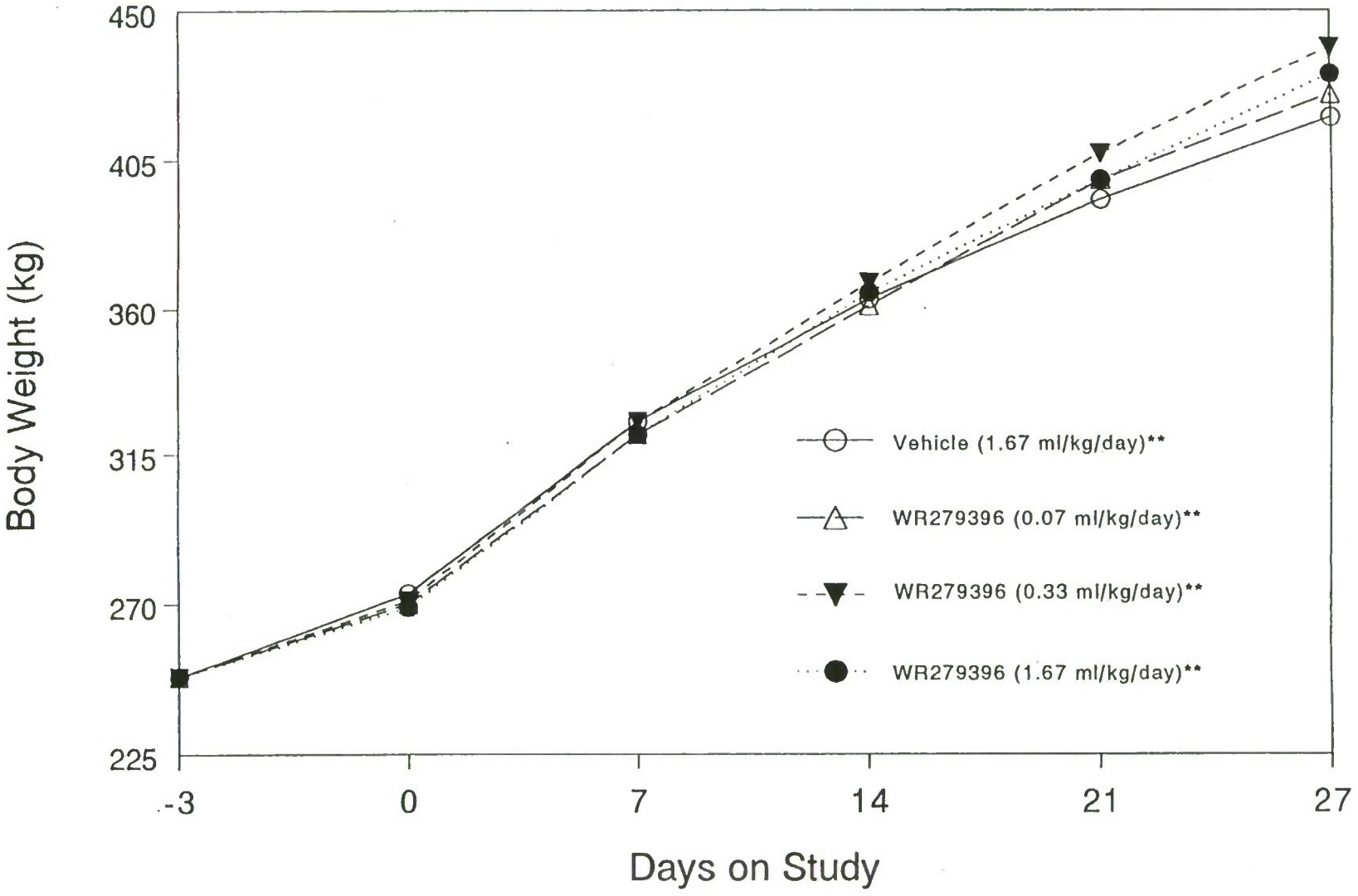
[c]On days 0 - 5, animals received twice the volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

For additional information see Pathology Report in Appendix 9.

Figure 1

FOUR WEEK TOXICITY STUDY OF WR279396 AFTER DAILY DERMAL APPLICATION IN CD® RATS

Summary of Male Body Weights

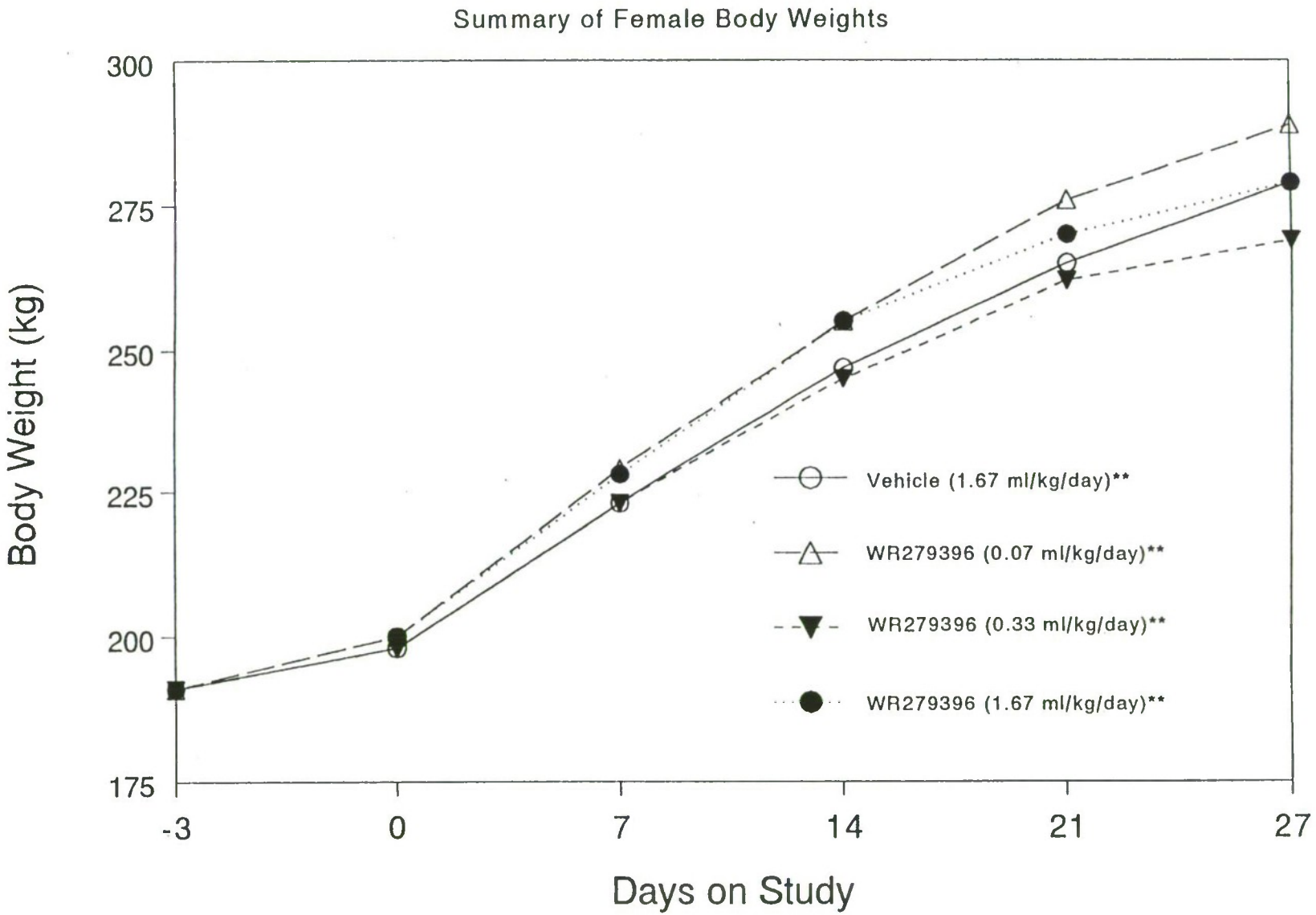


**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

Contract No.: DAMD17-92-C-2001
Task Order No.: UIC-12A
UIC/TRL Study NO.: 176

Figure 2

FOUR WEEK TOXICITY STUDY OF WR279396 AFTER DAILY DERMAL APPLICATION IN CD® RATS



**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

Contract No.: DAMD17-92-C-2001
Task Order No.: UIC-12A
UIC/TRL Study NO.: 176

APPENDIX 1

CLINICAL PATHOLOGY METHODOLOGY

CLINICAL CHEMISTRY

Alanine Aminotransferase (ALT)

Modified Wroblewski & La Due procedure
Ciba-Corning 550 Express Clinical Chemistry System
Henry, R.J., Chiamori, N., Golub, O.J. and Berkman, S.
Am. J. Clin. Path., 34, 381, 1960.

Sorbitol Dehydrogenase (SDH)

Fructose → Sorbitol oxidase reaction
Ciba-Corning 55 Express Clinical Chemistry System
Asada, M. and Galanbos J.T.
Gastroenterology 44, 578, 1963
Wiesner, I.S. *et al.*
Am. J. dig. Dis. 10, 147, 1965.

Total Protein

Biuret technique
Ciba-Corning 550 Express Clinical Chemistry System
Kingsley, G.R.
J. Biol. Chem. 131, 197, 1939.

Albumin

Bromocresol green method
Ciba-Corning 550 Express Clinical Chemistry System
Doumas, B.T. and Biggs, H.G.
Standard Methods of Clinical Chemistry, 7, 175, 1972.

Total Bile Acids

3α- Hydroxy bile acid oxidation procedure (Sigma Diagnostic kit)
Ciba-Corning 550 Express Clinical Chemistry System
Mashige, F. *et al.*
Clin. Chem. 27, 1352-1356, 1981.

Alkaline Phosphatase

Modified Bessey-Lowry procedure
Ciba-Corning 550 Express Clinical Chemistry System
Neumann, H. and Von Vreedendaal
M. Clin. Chem. Acta., 17, 183, 1967.

Cholesterol

Cholesterol esterase-oxidase method
Ciba-Corning 550 Express Clinical Chemistry System
Rosechlow, P., et. al
Z.F. Klin. Chem. V. Klin. Biochem. 12, 226, 1974.

Urea Nitrogen (BUN)

Modified urease technique
Ciba-Corning 550 Express Clinical Chemistry System
Talke, H. and Schubert, G.E.
Klin. Wchnschr. 43, 174, 1965.

Creatinine

Jaffe method
Ciba-Corning 550 Express Clinical Chemistry System
Larsen. K.
Clin. Chem. Acta, 41, 209, 1972

Na+, K+

Ion specific electrodes
Model 614 ISE Na+/K+ Analyzer (Ciba Corning)

Chloride

Mecuric thiocyanate procedure
Ciba-Corning 550 Express Clinical Chemistry System
Zall, O.M., Fisher, D. and Garner, M.Q.
Anal. Chem, 28, 1065, 1956.

Calcium

Modified alizarin procedure
Ciba-Corning 550 Express Clinical Chemistry System
Frings, C.S., et. al.
Clin. Chem., 16, 816, 1970.

Phosphorus, Inorganic

Ammonium molybdate method
Ciba-Corning 550 Express Clinical Chemistry System
Fiske, C.H. and Subbarow, Y.
J. Biol. Chem. 66, 325, 1925.

Glucose

Hexokinase method
Ciba-Corning 550 Express Clinical Chemistry System
Bondar, J.L. and Mead, D.C.
Clin. Chem. 20, 586, 1974.

HEMATOLOGY

Erythrocyte Count
Electronic counting procedure
Sysmex K1000 Hematology Analyzer

Hemoglobin
Cyanomethemoglobin method
Sysmex K1000 Hematology Analyzer

Hematocrit
Indirect method; calculated value based on volume of red cells and volume of blood

Mean Corpuscular Volume (MCV)
Indirect method; calculated value based on hematocrit and red blood cell count

Mean Corpuscular Hemoglobin (MCH)
Indirect method; calculated value based on erythrocyte count and hemoglobin

Mean Corpuscular Hemoglobin Concentration (MCHC)
Indirect method; calculated value based on hematocrit and hemoglobin

Reticulocyte Count
New methylene blue staining procedure
Brecher, G., Am. J. Clin. Path., 19, 895, 1949.

Platelet Count
Electronic counting procedure
Sysmex K1000 Hematology Analyzer

Leukocyte Count
Electronic counting procedure
Sysmex K1000 Hematology Analyzer

Leukocyte Differential Count
Neutrophils - Immature (bands)
Neutrophils - Mature (segs)
Monocytes
Basophils
Lymphocytes
Eosinophils
Wright stain procedure
Schalm, O.W., Jain, N.C. and Carroll, E.J. Veterinary Hematology, Color Plates Chapter, 3rd Edition, Lee and Febiger, 1975.

Nucleated RBCs
Wright stain procedure
Schalm, O.W., Jain, N.C. and Carroll, E.J. Veterinary Hematology, Color Plates Chapter, 3rd Edition, Lee and Febiger, 1975.

RBC Morphology
Wright stain procedure
Schalm, O.W., Jain, N.C. and Carroll, E.J. Veterinary Hematology, Color Plates Chapter, 3rd Edition, Lee and Febiger, 1975.

APPENDIX 2

INDIVIDUAL OBSERVATIONS (CLINICAL SIGNS)

INDIVIDUAL CLINICAL SIGNS

STUDY: 176 GROUP: 1-M SEX: MALE
DAY 0-DAY 29 DOSE: Vehicle (1.67 ml/kg/day)**

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
301	Normal 1st Sign			DAY 0-DAY 28
	Normal 2nd Sign			DAY 0-DAY 5
	Scheduled Sacrifice			DAY 29
302	Normal 1st Sign			DAY 0-DAY 28
	Normal 2nd Sign			DAY 0-DAY 5
	Scheduled Sacrifice			DAY 29
303	Normal 1st Sign			DAY 0-DAY 28
	Normal 2nd Sign			DAY 0-DAY 5
	Scheduled Sacrifice			DAY 29
304	Normal 1st Sign			DAY 0-DAY 28
	Normal 2nd Sign			DAY 0-DAY 5
	Scheduled Sacrifice			DAY 29
305	Normal 1st Sign			DAY 0-DAY 27
	Normal 2nd Sign			DAY 0-DAY 5
	Scheduled Sacrifice			DAY 28
306	Normal 1st Sign			DAY 0-DAY 28
	Normal 2nd Sign			DAY 0-DAY 5
	Scheduled Sacrifice			DAY 29
307	Normal 1st Sign			DAY 0-DAY 28
	Normal 2nd Sign			DAY 0-DAY 5
	Scheduled Sacrifice			DAY 29
308	Normal 1st Sign			DAY 0-DAY 28
	Normal 2nd Sign			DAY 0-DAY 5
	Scheduled Sacrifice			DAY 29
309	Normal 1st Sign			DAY 0-DAY 27
	Normal 2nd Sign			DAY 0-DAY 5
	Scheduled Sacrifice			DAY 28
310	Normal 1st Sign			DAY 0-DAY 28
	Normal 2nd Sign			DAY 0-DAY 5
	Scheduled Sacrifice			DAY 29

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

INDIVIDUAL CLINICAL SIGNS

STUDY: 176 GROUP: 2-M SEX: MALE
DAY 0-DAY 29 DOSE: WR279396 (0.07 ml/kg/day)**

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
321	Normal 1st Sign			DAY 0-DAY 27
	Normal 2nd Sign			DAY 0-DAY 5
	Scheduled Sacrifice			DAY 28
322	Normal 1st Sign			DAY 0-DAY 27
	Normal 2nd Sign			DAY 0-DAY 5
	Scheduled Sacrifice			DAY 28
323	Normal 1st Sign			DAY 0-DAY 28
	Normal 2nd Sign			DAY 0-DAY 5
	Scheduled Sacrifice			DAY 29
324	Normal 1st Sign			DAY 0-DAY 28
	Normal 2nd Sign			DAY 0-DAY 5
	Scheduled Sacrifice			DAY 29
325	Normal 1st Sign			DAY 0-DAY 27
	Normal 2nd Sign			DAY 0-DAY 5
	Scheduled Sacrifice			DAY 28
326	Normal 1st Sign			DAY 0-DAY 28
	Normal 2nd Sign			DAY 0-DAY 5
	Scheduled Sacrifice			DAY 29
327	Normal 1st Sign			DAY 0-DAY 27
	Normal 2nd Sign			DAY 0-DAY 5
	Scheduled Sacrifice			DAY 28
328	Normal 1st Sign			DAY 0-DAY 27
	Normal 2nd Sign			DAY 0-DAY 5
	Scheduled Sacrifice			DAY 28
329	Normal 1st Sign			DAY 0-DAY 28
	Normal 2nd Sign			DAY 0-DAY 5
	Scheduled Sacrifice			DAY 29
330	Accidental Death			DAY 23
	Normal 1st Sign			DAY 0-DAY 22
	Normal 2nd Sign			DAY 0-DAY 5

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

INDIVIDUAL CLINICAL SIGNS

STUDY: 176 GROUP: 3-M SEX: MALE
DAY 0-DAY 29 DOSE: WR279396 (0.33 ml/kg/day)**

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
341	Normal 1st Sign			DAY 0-DAY 28
	Normal 2nd Sign			DAY 0-DAY 5
	Scheduled Sacrifice			DAY 29
342	Normal 1st Sign			DAY 0-DAY 27
	Normal 2nd Sign			DAY 0-DAY 5
	Scheduled Sacrifice			DAY 28
343	Normal 1st Sign			DAY 0-DAY 27
	Normal 2nd Sign			DAY 0-DAY 5
	Scheduled Sacrifice			DAY 28
344	Normal 1st Sign			DAY 0-DAY 27
	Normal 2nd Sign			DAY 0-DAY 5
	Scheduled Sacrifice			DAY 28
345	Normal 1st Sign			DAY 0-DAY 28
	Normal 2nd Sign			DAY 0-DAY 5
	Scheduled Sacrifice			DAY 29
346	Normal 1st Sign			DAY 0-DAY 28
	Normal 2nd Sign			DAY 0-DAY 5
	Scheduled Sacrifice			DAY 29
347	Normal 1st Sign			DAY 0-DAY 27
	Normal 2nd Sign			DAY 0-DAY 5
	Scheduled Sacrifice			DAY 28
348	Normal 1st Sign			DAY 0-DAY 28
	Normal 2nd Sign			DAY 0-DAY 5
	Scheduled Sacrifice			DAY 29
349	Normal 1st Sign			DAY 0-DAY 28
	Normal 2nd Sign			DAY 0-DAY 5
	Scheduled Sacrifice			DAY 29
350	Normal 1st Sign			DAY 0-DAY 28
	Normal 2nd Sign			DAY 0-DAY 5
	Scheduled Sacrifice			DAY 29

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

INDIVIDUAL CLINICAL SIGNS

STUDY: 176 GROUP: 4-M SEX: MALE
DAY 0-DAY 29 DOSE: WR279396 (1.67 ml/kg/day)**

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
361	Normal 1st Sign			DAY 0-DAY 27
	Normal 2nd Sign			DAY 0-DAY 5
	Scheduled Sacrifice			DAY 28
362	Normal 1st Sign			DAY 0-DAY 28
	Normal 2nd Sign			DAY 0-DAY 5
	Scheduled Sacrifice			DAY 29
363	Normal 1st Sign			DAY 0-DAY 28
	Normal 2nd Sign			DAY 0-DAY 5
	Scheduled Sacrifice			DAY 29
364	Normal 1st Sign			DAY 0-DAY 27
	Normal 2nd Sign			DAY 0-DAY 5
	Scheduled Sacrifice			DAY 28
365	Normal 1st Sign			DAY 0-DAY 28
	Normal 2nd Sign			DAY 0-DAY 5
	Scheduled Sacrifice			DAY 29
366	Normal 1st Sign			DAY 0-DAY 28
	Normal 2nd Sign			DAY 0-DAY 5
	Scheduled Sacrifice			DAY 29
367	Normal 1st Sign			DAY 0-DAY 27
	Normal 2nd Sign			DAY 0-DAY 5
	Scheduled Sacrifice			DAY 28
368	Normal 1st Sign			DAY 0-DAY 27
	Normal 2nd Sign			DAY 0-DAY 5
	Scheduled Sacrifice			DAY 28
369	Normal 1st Sign			DAY 0-DAY 28
	Normal 2nd Sign			DAY 0-DAY 5
	Scheduled Sacrifice			DAY 29
370	Normal 1st Sign			DAY 0-DAY 27
	Normal 2nd Sign			DAY 0-DAY 5
	Scheduled Sacrifice			DAY 28

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

INDIVIDUAL CLINICAL SIGNS

STUDY: 176 GROUP: 1-F SEX: FEMALE
DAY 0-DAY 29 DOSE: Vehicle (1.67 ml/kg/day)**

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
311	Normal 1st Sign			DAY 0-DAY 27
	Normal 2nd Sign			DAY 0-DAY 5
	Scheduled Sacrifice			DAY 28
312	Normal 1st Sign			DAY 0-DAY 27
	Normal 2nd Sign			DAY 0-DAY 5
	Scheduled Sacrifice			DAY 28
313	Normal 1st Sign			DAY 0-DAY 28
	Normal 2nd Sign			DAY 0-DAY 5
	Scheduled Sacrifice			DAY 29
314	Normal 1st Sign			DAY 0-DAY 28
	Normal 2nd Sign			DAY 0-DAY 5
	Scheduled Sacrifice			DAY 29
315	Normal 1st Sign			DAY 0-DAY 28
	Normal 2nd Sign			DAY 0-DAY 5
	Scheduled Sacrifice			DAY 29
316	Normal 1st Sign			DAY 0-DAY 27
	Normal 2nd Sign			DAY 0-DAY 5
	Scheduled Sacrifice			DAY 28
317	Normal 1st Sign			DAY 0-DAY 27
	Normal 2nd Sign			DAY 0-DAY 5
	Scheduled Sacrifice			DAY 28
318	Normal 1st Sign			DAY 0-DAY 27
	Normal 2nd Sign			DAY 0-DAY 5
	Scheduled Sacrifice			DAY 28
319	Normal 1st Sign			DAY 0-DAY 27
	Normal 2nd Sign			DAY 0-DAY 5
	Scheduled Sacrifice			DAY 28
320	Normal 1st Sign			DAY 0-DAY 27
	Normal 2nd Sign			DAY 0-DAY 5
	Scheduled Sacrifice			DAY 28

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

INDIVIDUAL CLINICAL SIGNS

STUDY: 176 GROUP: 2-F SEX: FEMALE
DAY 0-DAY 29 DOSE: WR279396 (0.07 ml/kg/day)**

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
331	Normal 1st Sign			DAY 0-DAY 27
	Normal 2nd Sign			DAY 0-DAY 5
	Scheduled Sacrifice			DAY 28
332	Normal 1st Sign			DAY 0-DAY 27
	Normal 2nd Sign			DAY 0-DAY 5
	Scheduled Sacrifice			DAY 28
333	Normal 1st Sign			DAY 0-DAY 27
	Normal 2nd Sign			DAY 0-DAY 5
	Scheduled Sacrifice			DAY 28
334	Normal 1st Sign			DAY 0-DAY 28
	Normal 2nd Sign			DAY 0-DAY 5
	Scheduled Sacrifice			DAY 29
335	Normal 1st Sign			DAY 0-DAY 27
	Normal 2nd Sign			DAY 0-DAY 5
	Scheduled Sacrifice			DAY 28
336	Normal 1st Sign			DAY 0-DAY 28
	Normal 2nd Sign			DAY 0-DAY 5
	Scheduled Sacrifice			DAY 29
337	Normal 1st Sign			DAY 0-DAY 27
	Normal 2nd Sign			DAY 0-DAY 5
	Scheduled Sacrifice			DAY 28
338	Normal 1st Sign			DAY 0-DAY 28
	Normal 2nd Sign			DAY 0-DAY 5
	Scheduled Sacrifice			DAY 29
339	Normal 1st Sign			DAY 0-DAY 28
	Normal 2nd Sign			DAY 0-DAY 5
	Scheduled Sacrifice			DAY 29
340	Normal 1st Sign			DAY 0-DAY 28
	Normal 2nd Sign			DAY 0-DAY 5
	Scheduled Sacrifice			DAY 29

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

INDIVIDUAL CLINICAL SIGNS

STUDY: 176 GROUP: 3-F SEX: FEMALE
DAY 0-DAY 29 DOSE: WR279396 (0.33 ml/kg/day)**

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
351	Normal 1st Sign			DAY 0-DAY 28
	Normal 2nd Sign			DAY 0-DAY 5
	Scheduled Sacrifice			DAY 29
352	Normal 1st Sign			DAY 0-DAY 27
	Normal 2nd Sign			DAY 0-DAY 5
	Scheduled Sacrifice			DAY 28
353	Normal 1st Sign			DAY 0-DAY 27
	Normal 2nd Sign			DAY 0-DAY 5
	Scheduled Sacrifice			DAY 28
354	Normal 1st Sign			DAY 0-DAY 28
	Normal 2nd Sign			DAY 0-DAY 5
	Scheduled Sacrifice			DAY 29
355	Normal 1st Sign			DAY 0-DAY 28
	Normal 2nd Sign			DAY 0-DAY 5
	Scheduled Sacrifice			DAY 29
356	Normal 1st Sign			DAY 0-DAY 28
	Normal 2nd Sign			DAY 0-DAY 5
	Scheduled Sacrifice			DAY 29
357	Normal 1st Sign			DAY 0-DAY 27
	Normal 2nd Sign			DAY 0-DAY 5
	Scheduled Sacrifice			DAY 28
358	Normal 1st Sign			DAY 0-DAY 28
	Normal 2nd Sign			DAY 0-DAY 5
	Scheduled Sacrifice			DAY 29
359	Normal 1st Sign			DAY 0-DAY 28
	Normal 2nd Sign			DAY 0-DAY 5
	Scheduled Sacrifice			DAY 29
360	Normal 1st Sign			DAY 0-DAY 28
	Normal 2nd Sign			DAY 0-DAY 5
	Scheduled Sacrifice			DAY 29

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

INDIVIDUAL CLINICAL SIGNS

STUDY: 176 GROUP: 4-F SEX: FEMALE
DAY 0-DAY 29 DOSE: WR279396 (1.67 ml/kg/day)**

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
371	Normal 1st Sign			DAY 0-DAY 27
	Normal 2nd Sign			DAY 0-DAY 5
	Scheduled Sacrifice			DAY 28
372	Normal 1st Sign			DAY 0-DAY 28
	Normal 2nd Sign			DAY 0-DAY 5
	Scheduled Sacrifice			DAY 29
373	Normal 1st Sign			DAY 0-DAY 28
	Normal 2nd Sign			DAY 0-DAY 5
	Scheduled Sacrifice			DAY 29
374	Normal 1st Sign			DAY 0-DAY 27
	Normal 2nd Sign			DAY 0-DAY 5
	Scheduled Sacrifice			DAY 28
375	Normal 1st Sign			DAY 0-DAY 27
	Normal 2nd Sign			DAY 0-DAY 5
	Scheduled Sacrifice			DAY 28
376	Normal 1st Sign			DAY 0-DAY 27
	Normal 2nd Sign			DAY 0-DAY 5
	Scheduled Sacrifice			DAY 28
377	Normal 1st Sign			DAY 0-DAY 27
	Normal 2nd Sign			DAY 0-DAY 5
	Scheduled Sacrifice			DAY 28
378	Normal 1st Sign			DAY 0-DAY 27
	Normal 2nd Sign			DAY 0-DAY 5
	Scheduled Sacrifice			DAY 28
379	Normal 1st Sign			DAY 0-DAY 27
	Normal 2nd Sign			DAY 0-DAY 5
	Scheduled Sacrifice			DAY 28
380	Normal 1st Sign			DAY 0-DAY 27
	Normal 2nd Sign			DAY 0-DAY 5
	Scheduled Sacrifice			DAY 28

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

APPENDIX 3

INDIVIDUAL BODY WEIGHTS AND BODY WEIGHT GAINS

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 176 GROUP: 1-M SEX: MALE
DOSE: Vehicle (1.67 ml/kg/day)**

ANIMAL #	DAY -3	DAY 0	DAY 7	DAY 14	DAY 21	DAY 27
301	245	270	318	348	377	394
302	238	269	329	361	399	421
303	257	275	319	347	383	411
304	248	269	316	358	386	412
305	240	264	315	356	384	407
306	256	285	345	390	421	456
307	253	277	331	383	419	454
308	249	273	321	354	376	403
309	251	282	333	368	376	386
310	243	270	326	366	407	437
MEAN	248	273	325	363	393	418
S.D.	6.5	6.4	9.4	14.2	17.5	23.9
N	10	10	10	10	10	10

--: Data Unavailable

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 176 GROUP: 2-M SEX: MALE
DOSE: WR279396 (0.07 ml/kg/day)**

ANIMAL #	DAY -3	DAY 0	DAY 7	DAY 14	DAY 21	DAY 27
321	251	275	322	363	395	427
322	257	280	329	358	387	414
323	244	264	308	349	385	415
324	253	278	336	388	430	464
325	243	264	315	350	387	415
326	250	275	334	372	419	452
327	239	255	298	333	373	407
328	255	271	319	356	395	422
329	240	265	312	350	384	413
330	248	273	340	387	430	a
MEAN	248	270	321	361	399	425
S.D.	6.3	7.8	13.5	17.4	20.4	19.5
N	10	10	10	10	10	9

--: Data Unavailable a: Accidental Death

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 176 GROUP: 3-M SEX: MALE
DOSE: WR279396 (0.33 ml/kg/day)**

ANIMAL #	DAY -3	DAY 0	DAY 7	DAY 14	DAY 21	DAY 27
341	258	288	347	404	448	481
342	248	265	321	363	399	436
343	247	271	323	361	399	431
344	245	267	319	356	397	435
345	243	264	313	357	383	419
346	243	262	298	329	356	373
347	232	258	320	368	409	455
348	256	279	337	374	412	438
349	253	273	333	379	423	449
350	252	279	337	392	441	472
MEAN	248	271	325	368	407	439
S.D.	7.6	9.3	14.1	20.8	26.9	29.9
N	10	10	10	10	10	10

--: Data Unavailable

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 176 GROUP: 4-M SEX: MALE
DOSE: WR279396 (1.67 ml/kg/day)**

ANIMAL #	DAY -3	DAY 0	DAY 7	DAY 14	DAY 21	DAY 27
361	245	267	326	363	386	419
362	235	261	318	366	409	435
363	243	269	320	362	397	433
364	257	279	330	381	415	455
365	245	266	306	342	373	406
366	252	269	309	341	372	398
367	248	269	332	381	413	435
368	251	271	300	332	355	390
369	246	269	333	396	444	483
370	255	274	333	386	426	459
MEAN	248	269	321	365	399	431
S.D.	6.4	4.8	12.2	21.4	27.5	29.1
N	10	10	10	10	10	10

--: Data Unavailable

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 176 GROUP: 1-F SEX: FEMALE
DOSE: Vehicle (1.67 ml/kg/day)**

ANIMAL #	DAY -3	DAY 0	DAY 7	DAY 14	DAY 21	DAY 27
311	189	197	231	263	284	298
312	186	193	212	240	257	270
313	209	215	237	268	281	283
314	193	203	224	232	251	269
315	192	200	219	251	270	291
316	200	205	232	248	257	270
317	176	187	213	227	242	254
318	180	188	209	239	263	281
319	198	200	231	251	266	286
320	188	195	217	254	275	292
MEAN	191	198	223	247	265	279
S.D.	9.7	8.3	9.8	13.0	13.3	13.5
N	10	10	10	10	10	10

--: Data Unavailable

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 176 GROUP: 2-F SEX: FEMALE
DOSE: WR279396 (0.07 ml/kg/day)**

ANIMAL #	DAY -3	DAY 0	DAY 7	DAY 14	DAY 21	DAY 27
331	189	193	217	242	260	266
332	205	220	249	281	304	313
333	175	182	210	236	258	269
334	204	209	248	283	318	318
335	182	188	214	227	250	264
336	184	196	222	237	263	280
337	190	197	235	261	280	297
338	192	201	226	259	277	304
339	194	200	224	252	273	277
340	197	217	241	268	276	300
MEAN	191	200	229	255	276	289
S.D.	9.4	12.1	14.0	19.2	21.1	20.0
N	10	10	10	10	10	10

--: Data Unavailable

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 176 GROUP: 3-F SEX: FEMALE
DOSE: WR279396 (0.33 ml/kg/day)**

ANIMAL #	DAY -3	DAY 0	DAY 7	DAY 14	DAY 21	DAY 27
351	191	198	218	232	250	259
352	199	207	232	260	265	287
353	206	212	242	267	285	289
354	187	190	203	207	216	226
355	183	188	210	229	245	250
356	186	197	219	231	248	255
357	194	201	221	244	257	262
358	193	197	238	283	306	315
359	176	189	214	233	254	255
360	195	204	235	265	291	296
MEAN	191	198	223	245	262	269
S.D.	8.5	7.9	12.9	23.0	26.1	26.5
N	10	10	10	10	10	10

--: Data Unavailable

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 176 GROUP: 4-F SEX: FEMALE
DOSE: WR279396 (1.67 ml/kg/day)**

ANIMAL #	DAY -3	DAY 0	DAY 7	DAY 14	DAY 21	DAY 27
371	192	206	232	257	264	283
372	193	206	233	255	274	282
373	208	211	238	268	285	296
374	187	194	227	249	266	270
375	201	213	240	271	289	301
376	182	187	224	252	265	278
377	192	197	246	275	307	330
378	197	198	213	247	257	258
379	183	193	214	232	239	239
380	176	192	213	239	251	255
MEAN	191	200	228	255	270	279
S.D.	9.5	8.8	11.9	13.8	19.8	26.0
N	10	10	10	10	10	10

--: Data Unavailable

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD® RATS

INDIVIDUAL WEIGHT GAIN (Grams)[a]

STUDY: 176 GROUP: 1-M SEX: MALE
DOSE: Vehicle (1.67 ml/kg/day)**

ANIMAL #	DAY 7[b]	DAY 14	DAY 21	DAY 27	TOTAL GAIN
301	48	30	29	17	124
302	60	32	38	22	152
303	44	28	36	28	136
304	47	42	28	26	143
305	51	41	28	23	143
306	60	45	31	35	171
307	54	52	36	35	177
308	48	33	22	27	130
309	51	35	8	10	104
310	56	40	41	30	167
MEAN	52	38	30	25	145
S.D.	5.5	7.5	9.5	7.7	22.8
N	10	10	10	10	10

--: Data Unavailable

[a] Successive periods

[b] Baseline is day 0

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

INDIVIDUAL WEIGHT GAIN (Grams)[b]

STUDY: 176 GROUP: 2-M SEX: MALE
DOSE: WR279396 (0.07 ml/kg/day)**

ANIMAL #	DAY 7[c]	DAY 14	DAY 21	DAY 27	TOTAL GAIN
321	47	41	32	32	152
322	49	29	29	27	134
323	44	41	36	30	151
324	58	52	42	34	186
325	51	35	37	28	151
326	59	38	47	33	177
327	43	35	40	34	152
328	48	37	39	27	151
329	47	38	34	29	148
330	67	47	43	a	--
MEAN	51	39	38	30	156
S.D.	7.6	6.5	5.4	2.9	15.8
N	10	10	10	9	9

--: Data Unavailable a: Accidental Death

[b] Successive periods

[c] Baseline is day 0

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD® RATS

INDIVIDUAL WEIGHT GAIN (Grams)[a]

STUDY: 176 GROUP: 3-M SEX: MALE
DOSE: WR279396 (0.33 ml/kg/day)**

ANIMAL #	DAY 7[b]	DAY 14	DAY 21	DAY 27	TOTAL GAIN
341	59	57	44	33	193
342	56	42	36	37	171
343	52	38	38	32	160
344	52	37	41	38	168
345	49	44	26	36	155
346	36	31	27	17	111
347	62	48	41	46	197
348	58	37	38	26	159
349	60	46	44	26	176
350	58	55	49	31	193
MEAN	54	44	38	32	168
S.D.	7.6	8.3	7.3	8.0	25.2
N	10	10	10	10	10

--: Data Unavailable

[a]Successive periods

[b]Baseline is day 0

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

INDIVIDUAL WEIGHT GAIN (Grams)[a]

STUDY: 176 GROUP: 4-M SEX: MALE
DOSE: WR279396 (1.67 ml/kg/day)**

ANIMAL #	DAY 7[b]	DAY 14	DAY 21	DAY 27	TOTAL GAIN
361	59	37	23	33	152
362	57	48	43	26	174
363	51	42	35	36	164
364	51	51	34	40	176
365	40	36	31	33	140
366	40	32	31	26	129
367	63	49	32	22	166
368	29	32	23	35	119
369	64	63	48	39	214
370	59	53	40	33	185
MEAN	51	44	34	32	162
S.D.	11.6	10.2	8.0	5.9	28.1
N	10	10	10	10	10

--: Data Unavailable

[a] Successive periods

[b] Baseline is day 0

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

INDIVIDUAL WEIGHT GAIN (Grams)[a]

STUDY: 176 GROUP: 1-F SEX: FEMALE
DOSE: Vehicle (1.67 ml/kg/day)**

ANIMAL #	DAY 7[b]	DAY 14	DAY 21	DAY 27	TOTAL GAIN
311	34	32	21	14	101
312	19	28	17	13	77
313	22	31	13	2	68
314	21	8	19	18	66
315	19	32	19	21	91
316	27	16	9	13	65
317	26	14	15	12	67
318	21	30	24	18	93
319	31	20	15	20	86
320	22	37	21	17	97
MEAN	24	25	17	15	81
S.D.	5.1	9.6	4.4	5.5	14.1
N	10	10	10	10	10

--: Data Unavailable

[a]Successive periods

[b]Baseline is day 0

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD® RATS

INDIVIDUAL WEIGHT GAIN (Grams)[a]

STUDY: 176 GROUP: 2-F SEX: FEMALE
DOSE: WR279396 (0.07 ml/kg/day)**

ANIMAL #	DAY 7[b]	DAY 14	DAY 21	DAY 27	TOTAL GAIN
331	24	25	18	6	73
332	29	32	23	9	93
333	28	26	22	11	87
334	39	35	35	0	109
335	26	13	23	14	76
336	26	15	26	17	84
337	38	26	19	17	100
338	25	33	18	27	103
339	24	28	21	4	77
340	24	27	8	24	83
MEAN	28	26	21	13	89
S.D.	5.6	7.2	6.8	8.6	12.3
N	10	10	10	10	10

--: Data Unavailable

[a] Successive periods

[b] Baseline is day 0

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD® RATS

INDIVIDUAL WEIGHT GAIN (Grams)[a]

STUDY: 176 GROUP: 3-F SEX: FEMALE
DOSE: WR279396 (0.33 ml/kg/day)**

ANIMAL #	DAY 7[b]	DAY 14	DAY 21	DAY 27	TOTAL GAIN
351	20	14	18	9	61
352	25	28	5	22	80
353	30	25	18	4	77
354	13	4	9	10	36
355	22	19	16	5	62
356	22	12	17	7	58
357	20	23	13	5	61
358	41	45	23	9	118
359	25	19	21	1	66
360	31	30	26	5	92
MEAN	25	22	17	8	71
S.D.	7.7	11.3	6.3	5.7	22.3
N	10	10	10	10	10

--: Data Unavailable

[a]Successive periods

[b]Baseline is day 0

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

INDIVIDUAL WEIGHT GAIN (Grams)[a]

STUDY: 176 GROUP: 4-F SEX: FEMALE
DOSE: WR279396 (1.67 ml/kg/day)**

ANIMAL #	DAY 7[b]	DAY 14	DAY 21	DAY 27	TOTAL GAIN
371	26	25	7	19	77
372	27	22	19	8	76
373	27	30	17	11	85
374	33	22	17	4	76
375	27	31	18	12	88
376	37	28	13	13	91
377	49	29	32	23	133
378	15	34	10	1	60
379	21	18	7	0	46
380	21	26	12	4	63
MEAN	28	27	15	10	80
S.D.	9.5	4.9	7.4	7.6	23.3
N	10	10	10	10	10

--: Data Unavailable

[a] Successive periods

[b] Baseline is day 0

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

APPENDIX 4

INDIVIDUAL FOOD CONSUMPTION DATA

INDIVIDUAL DAILY FOOD CONSUMPTION (Grams)[a]

STUDY: 176 GROUP: 1-M SEX: MALE
DOSE:[b] Vehicle (1.67 ml/kg/day)**

ANIMAL #	DAY 0[b]	DAY 7	DAY 14	DAY 21	DAY 27
301	23	26	24	23	27
302	23	27	28	27	27
303	23	26	25	25	26
304	22	24	25	24	25
305	25	28	27	26	25
306	24	28	28	27	29
307	23	27	28	27	28
308	25	27	27	26	27
309	23	27	26	23	11
310	22	26	25	26	26
MEAN	23	27	26	25	25
S.D.	1.1	1.2	1.5	1.6	5.1
N	10	10	10	10	10

--: Data Unavailable

[a] Inclusive intervals

[b] Food in on day -6

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

INDIVIDUAL DAILY FOOD CONSUMPTION (Grams)[b]

STUDY: 176 GROUP: 2-M SEX: MALE
DOSE: WR279396 (0.07 ml/kg/day)**

ANIMAL #	DAY 0 [c]	DAY 7	DAY 14	DAY 21	DAY 27
321	24	27	26	26	27
322	23	26	25	24	25
323	22	24	24	24	25
324	25	29	29	28	29
325	23	26	26	25	26
326	23	28	27	28	28
327	22	24	23	24	25
328	22	26	26	25	27
329	23	27	25	25	28
330	23	29	28	28	a
MEAN	23	27	26	26	27
S.D.	0.9	1.8	1.8	1.7	1.5
N	10	10	10	10	9

--: Data Unavailable a: Accidental Death

[b] Inclusive intervals

[c] Food in on day -6

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

INDIVIDUAL DAILY FOOD CONSUMPTION (Grams)[a]

STUDY: 176 GROUP: 3-M SEX: MALE
DOSE: WR279396 (0.33 ml/kg/day)**

ANIMAL #	DAY 0[b]	DAY 7	DAY 14	DAY 21	DAY 27
341	25	--	29	29	29
342	21	25	26	25	27
343	21	27	25	27	27
344	22	26	24	25	25
345	22	26	25	26	29
346	23	24	23	23	23
347	21	25	26	27	28
348	24	27	27	28	30
349	23	27	28	28	27
350	26	28	30	31	31
MEAN	23	26	26	27	28
S.D.	1.8	1.3	2.2	2.3	2.4
N	10	9	10	10	10

--: Data Unavailable

[a]Inclusive intervals

[b]Food in on day -6

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

INDIVIDUAL DAILY FOOD CONSUMPTION (Grams)[a]

STUDY: 176 GROUP: 4-M SEX: MALE
DOSE: WR279396 (1.67 ml/kg/day)**

ANIMAL #	DAY 0[b]	DAY 7	DAY 14	DAY 21	DAY 27
361	22	26	26	25	28
362	21	27	30	29	30
363	23	27	29	28	31
364	24	28	28	28	30
365	23	26	26	25	29
366	24	26	24	25	32
367	26	29	29	28	29
368	23	23	24	23	27
369	23	27	31	31	34
370	23	29	31	30	33
MEAN	23	27	28	27	30
S.D.	1.3	1.8	2.7	2.6	2.2
N	10	10	10	10	10

--: Data Unavailable

[a] Inclusive intervals

[b] Food in on day -6

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

INDIVIDUAL DAILY FOOD CONSUMPTION (Grams)[a]

STUDY: 176 GROUP: 1-F SEX: FEMALE
DOSE: Vehicle (1.67 ml/kg/day)**

ANIMAL #	DAY 0 [b]	DAY 7	DAY 14	DAY 21	DAY 27
311	17	21	21	21	23
312	16	19	20	19	23
313	18	20	21	19	19
314	19	22	21	20	24
315	17	20	20	20	28
316	18	21	22	19	20
317	15	20	20	20	21
318	18	25	23	22	31
319	16	20	19	19	20
320	17	20	22	21	24
MEAN	17	21	21	20	23
S.D.	1.2	1.7	1.2	1.1	3.8
N	10	10	10	10	10

--: Data Unavailable

[a] Inclusive intervals

[b] Food in on day -6

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

INDIVIDUAL DAILY FOOD CONSUMPTION (Grams)[a]

STUDY: 176 GROUP: 2-F SEX: FEMALE
DOSE: WR279396 (0.07 ml/kg/day)**

ANIMAL #	DAY 0[b]	DAY 7	DAY 14	DAY 21	DAY 27
331	17	21	20	20	26
332	19	22	23	21	22
333	16	18	19	20	21
334	20	22	23	24	22
335	16	19	19	20	19
336	16	19	18	20	21
337	17	22	21	24	28
338	17	21	22	21	25
339	17	20	20	19	22
340	18	20	22	21	21
MEAN	17	20	21	21	23
S.D.	1.3	1.4	1.8	1.7	2.8
N	10	10	10	10	10

--: Data Unavailable

[a] Inclusive intervals

[b] Food in on day -6

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

INDIVIDUAL DAILY FOOD CONSUMPTION (Grams)[a]

STUDY: 176 GROUP: 3-F SEX: FEMALE
DOSE: WR279396 (0.33 ml/kg/day)**

ANIMAL #	DAY 0[b]	DAY 7	DAY 14	DAY 21	DAY 27
351	17	19	19	19	22
352	18	21	21	20	25
353	19	20	22	21	20
354	14	16	15	15	16
355	16	18	20	18	18
356	16	18	19	18	18
357	17	19	20	19	19
358	19	21	26	27	24
359	15	18	19	19	20
360	18	21	23	24	26
MEAN	17	19	20	20	21
S.D.	1.7	1.7	2.9	3.4	3.3
N	10	10	10	10	10

--: Data Unavailable

[a] Inclusive intervals

[b] Food in on day -6

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

INDIVIDUAL DAILY FOOD CONSUMPTION (Grams)[a]

STUDY: 176 GROUP: 4-F SEX: FEMALE
DOSE: WR279396 (1.67 ml/kg/day)**

ANIMAL #	DAY 0 [b]	DAY 7	DAY 14	DAY 21	DAY 27
371	18	20	21	19	22
372	18	20	22	21	23
373	18	20	23	21	23
374	16	20	20	19	22
375	19	21	23	21	29
376	16	19	20	19	20
377	18	24	25	26	33
378	16	18	20	18	19
379	16	19	20	18	21
380	16	19	20	18	19
MEAN	17	20	21	20	23
S.D.	1.2	1.6	1.8	2.4	4.5
N	10	10	10	10	10

--: Data Unavailable

[a] Inclusive intervals

[b] Food in on day -6

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD® RATS

INDIVIDUAL FOOD CONSUMPTION (Grams)[a]

STUDY: 176 GROUP: 1-M SEX: MALE
DOSE:[b] Vehicle (1.67 ml/kg/day)**

ANIMAL #	DAY 0	DAY 7	DAY 14	DAY 21	DAY 27
301	139	183	169	164	163
302	137	188	194	188	163
303	139	181	175	175	154
304	132	171	177	166	152
305	149	197	188	184	148
306	143	193	199	191	175
307	140	188	196	192	165
308	150	191	189	180	164
309	140	190	181	163	68
310	134	183	176	179	158
MEAN	140	187	184	178	151
S.D.	5.8	7.3	10.2	11.0	30.2
N	10	10	10	10	10

--: Data Unavailable

[a] Inclusive intervals

[b] Food in on day -6

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

INDIVIDUAL FOOD CONSUMPTION (Grams)[b]

STUDY: 176 GROUP: 2-M SEX: MALE
DOSE: WR279396 (0.07 ml/kg/day)**

ANIMAL #	DAY 0[c]	DAY 7	DAY 14	DAY 21	DAY 27
321	141	188	181	181	164
322	136	183	173	169	147
323	132	168	166	168	149
324	150	200	202	199	175
325	135	181	183	175	154
326	138	195	190	193	169
327	132	169	162	168	149
328	130	181	182	173	163
329	138	192	175	176	166
330	137	202	198	198	a
MEAN	137	186	181	180	160
S.D.	5.7	11.8	12.9	12.3	10.1
N	10	10	10	10	9

--: Data Unavailable a: Accidental Death

[b] Inclusive intervals

[c] Food in on day -6

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

INDIVIDUAL FOOD CONSUMPTION (Grams)[a]

STUDY: 176 GROUP: 3-M SEX: MALE
DOSE: WR279396 (0.33 ml/kg/day)**

ANIMAL #	DAY 0 [b]	DAY 7	DAY 14	DAY 21	DAY 27
341	150	--	206	200	174
342	127	174	184	174	163
343	128	188	176	186	162
344	130	181	171	172	152
345	131	179	173	179	174
346	135	165	162	158	138
347	128	178	180	188	167
348	143	191	186	196	181
349	137	188	195	196	163
350	153	196	208	215	183
MEAN	136	182	184	186	166
S.D.	9.5	9.5	15.1	16.4	13.6
N	10	9	10	10	10

--: Data Unavailable

[a] Inclusive intervals

[b] Food in on day -6

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

INDIVIDUAL FOOD CONSUMPTION (Grams)[a]

STUDY: 176 GROUP: 4-M SEX: MALE
DOSE: WR279396 (1.67 ml/kg/day)**

ANIMAL #	DAY 0[b]	DAY 7	DAY 14	DAY 21	DAY 27
361	132	181	185	175	165
362	125	188	210	204	182
363	136	191	201	196	188
364	144	193	195	199	181
365	137	179	184	177	175
366	146	182	170	176	190
367	155	202	206	193	175
368	135	163	169	160	161
369	135	188	217	214	204
370	135	201	214	210	200
MEAN	138	187	195	190	182
S.D.	8.3	11.4	17.5	17.6	13.9
N	10	10	10	10	10

--: Data Unavailable

[a] Inclusive intervals

[b] Food in on day -6

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

INDIVIDUAL FOOD CONSUMPTION (Grams)[a]

STUDY: 176 GROUP: 1-F SEX: FEMALE
DOSE: Vehicle (1.67 ml/kg/day)**

ANIMAL #	DAY 0 [b]	DAY 7	DAY 14	DAY 21	DAY 27
311	104	150	150	149	139
312	95	134	137	134	136
313	109	141	148	133	116
314	116	151	146	143	142
315	99	143	140	139	166
316	106	147	151	131	120
317	91	137	141	140	126
318	106	176	160	156	184
319	97	140	133	130	121
320	101	137	151	150	143
MEAN	102	146	146	141	139
S.D.	7.3	12.1	8.0	8.9	21.5
N	10	10	10	10	10

--: Data Unavailable

[a] Inclusive intervals

[b] Food in on day -6

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

INDIVIDUAL FOOD CONSUMPTION (Grams)[a]

STUDY: 176 GROUP: 2-F SEX: FEMALE
DOSE: WR279396 (0.07 ml/kg/day)**

ANIMAL #	DAY 0 [b]	DAY 7	DAY 14	DAY 21	DAY 27
331	100	147	143	142	158
332	114	153	162	144	132
333	96	129	134	139	124
334	121	153	163	170	129
335	97	131	135	138	112
336	96	131	126	141	123
337	100	151	149	165	167
338	103	149	155	148	148
339	102	137	143	135	129
340	110	143	151	144	126
MEAN	104	142	146	147	135
S.D.	8.4	9.6	12.2	11.6	17.2
N	10	10	10	10	10

--: Data Unavailable

[a] Inclusive intervals

[b] Food in on day -6

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

INDIVIDUAL FOOD CONSUMPTION (Grams)[a]

STUDY: 176 GROUP: 3-F SEX: FEMALE
DOSE: WR279396 (0.33 ml/kg/day)**

ANIMAL #	DAY 0[b]	DAY 7	DAY 14	DAY 21	DAY 27
351	102	130	134	136	129
352	107	146	146	137	148
353	115	140	156	144	119
354	82	113	106	107	98
355	97	128	139	124	110
356	97	127	131	123	110
357	99	135	137	133	115
358	115	148	180	189	145
359	91	125	131	135	121
360	105	145	159	165	153
MEAN	101	134	142	139	125
S.D.	10.2	11.2	19.9	23.0	18.4
N	10	10	10	10	10

--: Data Unavailable

[a] Inclusive intervals

[b] Food in on day -6

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

INDIVIDUAL FOOD CONSUMPTION (Grams)[a]

STUDY: 176 GROUP: 4-F SEX: FEMALE
DOSE:[b] WR279396 (1.67 ml/kg/day)**

ANIMAL #	DAY 0	DAY 7	DAY 14	DAY 21	DAY 27
371	105	139	149	133	131
372	107	142	152	144	136
373	107	140	160	148	139
374	97	138	142	136	130
375	113	146	158	150	171
376	95	133	143	135	119
377	110	167	175	179	199
378	94	125	141	124	112
379	95	133	140	125	125
380	95	132	139	124	113
MEAN	102	140	150	140	138
S.D.	7.3	11.3	11.6	16.8	27.4
N	10	10	10	10	10

--: Data Unavailable

[a] Inclusive intervals

[b] Food in on day -6

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

APPENDIX 5

INDIVIDUAL CLINICAL CHEMISTRY DATA

Clinical Chemistry Test Directory

STUDY: UIC-12A

NO.	ABBR. / UNITS	DESCRIPTION / PRECISION	CALCULATED	OPERAND A	OPERAND B	---LOWER LIMIT--- MALE	---LOWER LIMIT--- FEMALE	---UPPER LIMIT--- MALE	---UPPER LIMIT--- FEMALE
1.	ALT	Alanine Aminotransferase							
	IU/L	Integer	NO			30	30	70	70
2.	SDH	Sorbitol Dehydrogenase							
	IU/L	0.0	NO			10	10	30	30
3.	TP	Total Protein							
	g/dL	0.0	NO			6.0	6.0	9.5	9.5
4.	ALB	Albumin							
	g/dL	0.0	NO			3.4	3.4	5.6	5.6
5.	TBA	Total Bile Acids							
	umol/L	0.0	NO			25.0	25.0	75.0	75.0
6.	ALKP	Alkaline Phosphatase							
	IU/L	Integer	NO			60	40	500	250
7.	CHOL	Cholesterol							
	mg/dL	Integer	NO			25	25	75	75
8.	BUN	Blood Urea Nitrogen							
	mg/dL	0.0	NO			12.0	12.0	22.0	22.0
9.	CREAT	Creatinine							
	mg/dL	0.00	NO			0.40	0.40	0.80	0.80
10.	NA	Sodium							
	mEq/L	Integer	NO			140	140	148	148
11.	K	Potassium							
	mEq/L	0.00	NO			5.00	5.00	7.00	7.00
12.	CL	Chloride							
	mEq/L	Integer	NO			95	95	115	115
13.	CA	Calcium							
	mg/dL	0.0	NO			9.0	9.0	12.0	12.0
14.	IP	Inorganic Phosphorus							
	mg/dL	0.0	NO			5.5	5.5	11.0	11.0
15.	GLU	Glucose							
	mg/dL	Integer	NO			80	80	175	175
16.	GLOB	Globulin							
	g/dL	0.0	Operand A - Operand B	TP	ALB	2.5	2.5	5.0	5.0

(END OF REPORT)

08-JUN-1995

FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD® RATS

IND. ANIMAL CLINICAL CHEMISTRY REPORT BY GROUP
PERIOD: DAY27/28

STUDY ID: UIC-12A
STUDY NO: 176
SEX: MALE

Animal ID	ALT IU/L	SDH IU/L	TP g/dL	ALB g/dL	GLOB g/dL	TBA umol/L	ALKP IU/L	CHOL mg/dL
GROUP: 1-M:VEHICLE (1.67 ml/kg/day)**								
301	59	12.4	7.6	4.0	3.6	19.3	479	72
302	64	7.2	7.6	4.0	3.6	63.2	336	60
303	52	14.6	7.0	4.0	3.0	49.9	279	81
304	61	14.8	7.5	4.3	3.2	83.5	426	59
305	54	20.3	7.7	4.0	3.7	31.7	435	47
306	68	11.3	7.8	4.0	3.8	23.0	554	77
307	97	11.1	7.6	4.3	3.3	48.7	535	65
308	62	14.2	7.5	3.7	3.8	24.7	413	70
309	113	16.4	6.9	3.7	3.2	40.1	262	75
310	53	12.1	7.0	4.0	3.0	43.9	481	42
MEAN	68	13.4	7.4	4.0	3.4	42.8	420	65
SD	20.3	3.52	0.33	0.20	0.32	19.89	100.3	12.9
N	10	10	10	10	10	10	10	10
GROUP: 2-M:WR279396 (0.07 ml/kg/day)**								
321	44	11.7	7.4	3.5	3.9	17.7	259	74
322	48	17.4	7.9	3.8	4.1	20.4	546	70
323	63	1.2	7.5	4.2	3.3	59.2	272	62
324	62	8.6	7.0	3.9	3.1	20.4	364	86
325	53	18.7	7.5	4.1	3.4	28.2	339	71
326	67	15.3	8.1	4.4	3.7	70.6	420	62
327	60	5.9	7.1	3.8	3.3	39.0	498	68
328	50	18.3	7.4	4.1	3.3	29.2	295	79
329	57	11.6	7.2	4.1	3.1	79.3	346	73
330	--	--	--	--	--	--	--	--
MEAN	56	12.1	7.5	4.0	3.5	40.4	371	72
SD	7.7	6.02	0.36	0.27	0.35	23.37	99.4	7.7
N	9	9	9	9	9	9	9	9

(--) - Data Unavailable

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD® RATS

IND. ANIMAL CLINICAL CHEMISTRY REPORT BY GROUP
PERIOD: DAY27/28

STUDY ID: UIC-12A
STUDY NO: 176
SEX: MALE

Animal ID	ALT IU/L	SDH IU/L	TP g/dL	ALB g/dL	GLOB g/dL	TBA umol/L	ALKP IU/L	CHOL mg/dL
GROUP: 3-M:WR279396 (0.33 ml/kg/day)**								
341	60	6.1	7.8	4.2	3.6	30.6	431	69
342	46	13.2	7.6	3.9	3.7	31.2	450	71
343	59	11.3	7.7	3.9	3.8	20.2	411	57
344	40	13.8	6.9	3.8	3.1	68.0	265	66
345	50	12.2	7.3	3.9	3.4	18.2	247	58
346	71	12.3	7.6	4.2	3.4	28.2	389	63
347	54	15.0	7.9	4.1	3.8	19.9	365	74
348	67	9.5	7.3	4.0	3.3	18.9	534	73
349	61	7.2	7.3	3.7	3.6	31.3	307	62
350	67	3.7	8.1	4.6	3.5	17.4	470	78
MEAN	58	10.4	7.6	4.0	3.5	28.4	387	67
SD	9.9	3.69	0.35	0.26	0.23	15.07	92.1	7.1
N	10	10	10	10	10	10	10	10
GROUP: 4-M:WR279396 (1.67 ml/kg/day)**								
361	55	6.9	7.8	4.1	3.7	36.2	397	78
362	51	14.3	7.5	4.3	3.2	36.9	301	76
363	61	8.5	8.2	4.6	3.6	22.9	367	83
364	47	14.7	7.7	3.9	3.8	11.3	315	82
365	59	13.2	6.6	3.9	2.7	20.0	425	75
366	68	14.2	7.6	4.2	3.4	76.1	407	72
367	48	1.1	7.4	3.7	3.7	23.6	336	69
368	108	4.5	7.3	3.9	3.4	24.5	408	65
369	46	7.5	7.0	4.0	3.0	18.4	280	86
370	81	13.7	7.2	3.7	3.5	33.3	451	63
MEAN	62	9.9	7.4	4.0	3.4	30.3	369	75
SD	19.3	4.82	0.44	0.28	0.35	18.03	57.9	7.7
N	10	10	10	10	10	10	10	10

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD® RATS

IND. ANIMAL CLINICAL CHEMISTRY REPORT BY GROUP
PERIOD: DAY27/28

STUDY ID: UIC-12A
STUDY NO: 176
SEX: MALE

Animal ID	BUN mg/dL	CREAT mg/dL	NA mEq/L	K mEq/L	CL mEq/L	CA mg/dL	IP mg/dL	GLU mg/dL
GROUP: 1-M:VEHICLE (1.67 ml/kg/day)**								
301	13.9	0.55	145	5.97	108	10.2	9.7	150
302	15.5	0.52	142	5.87	106	11.1	9.9	148
303	16.5	0.49	144	5.78	107	11.2	10.8	151
304	15.8	0.55	142	5.35	107	10.7	9.4	150
305	15.6	0.54	145	5.89	100	10.0	7.4	138
306	15.7	0.55	145	5.84	109	10.9	10.0	153
307	19.1	0.67	145	4.32	113	11.7	10.4	227
308	19.2	0.55	144	5.92	108	10.8	10.2	145
309	13.9	0.57	147	6.29	108	10.2	9.1	132
310	17.8	0.52	144	5.44	109	10.1	9.6	155
MEAN	16.3	0.55	144	5.67	108	10.7	9.7	155
SD	1.88	0.047	1.5	0.542	3.2	0.56	0.93	26.3
N	10	10	10	10	10	10	10	10
GROUP: 2-M:WR279396 (0.07 ml/kg/day)**								
321	13.3	0.45	144	5.94	103	10.7	8.2	138
322	12.9	0.51	146	6.28	99	10.4	8.2	131
323	19.1	0.57	142	5.65	113	11.7	10.3	169
324	18.8	0.53	144	5.71	108	10.8	9.0	147
325	12.5	0.49	144	6.54	101	9.9	10.2	154
326	22.3	0.62	143	4.43	117	11.4	11.1	250
327	16.3	0.53	143	7.43	104	10.7	8.0	157
328	15.5	0.54	144	6.09	105	10.8	9.2	159
329	17.3	0.54	144	5.36	106	11.0	9.1	147
330	--	--	--	--	--	--	--	--
MEAN	16.4	0.53	144	5.94	106	10.8	9.3	161
SD	3.29	0.048	1.1	0.827	5.7	0.52	1.08	35.1
N	9	9	9	9	9	9	9	9

(--) - Data Unavailable

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD® RATS

IND. ANIMAL CLINICAL CHEMISTRY REPORT BY GROUP
PERIOD: DAY27/28

STUDY ID: UIC-12A
STUDY NO: 176
SEX: MALE

Animal ID	BUN mg/dL	CREAT mg/dL	NA mEq/L	K mEq/L	CL mEq/L	CA mg/dL	IP mg/dL	GLU mg/dL
GROUP: 3-M:WR279396 (0.33 ml/kg/day)**								
341	17.0	0.67	144	4.73	110	11.7	11.4	246
342	15.3	0.55	143	5.84	104	10.4	9.9	147
343	13.8	0.54	145	6.10	102	10.6	8.5	124
344	13.8	0.48	143	6.11	99	10.8	8.9	137
345	17.6	0.46	145	5.71	106	10.3	9.6	155
346	16.4	0.57	145	5.51	107	11.1	9.1	139
347	19.7	0.53	143	6.36	105	11.0	9.4	152
348	17.5	0.58	145	5.75	111	10.5	9.6	157
349	15.0	0.54	144	4.54	106	10.7	10.1	177
350	18.5	0.61	146	6.05	107	11.4	9.6	141
MEAN	16.5	0.55	144	5.67	106	10.9	9.6	158
SD	1.97	0.060	1.1	0.598	3.5	0.45	0.79	34.2
N	10	10	10	10	10	10	10	10
GROUP: 4-M:WR279396 (1.67 ml/kg/day)**								
361	16.3	0.51	144	6.02	103	10.9	9.5	145
362	23.1	0.56	148	4.29	107	11.0	9.7	247
363	18.2	0.57	145	6.27	109	10.4	9.9	142
364	15.4	0.54	147	5.53	98	10.6	8.6	142
365	18.4	0.49	141	5.26	105	10.9	8.8	152
366	20.3	0.66	147	4.26	113	11.8	10.8	246
367	16.8	0.46	144	7.37	103	13.2	7.9	148
368	16.8	0.58	145	6.81	101	10.5	10.7	147
369	21.8	0.50	142	5.83	112	11.4	11.3	185
370	17.9	0.50	142	6.34	109	10.1	10.5	174
MEAN	18.5	0.54	145	5.80	106	11.1	9.8	173
SD	2.49	0.058	2.4	1.003	4.9	0.89	1.09	41.4
N	10	10	10	10	10	10	10	10

**On days 0.- 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

IND. ANIMAL CLINICAL CHEMISTRY REPORT BY GROUP
PERIOD: DAY27/28

STUDY ID: UIC-12A
STUDY NO: 176
SEX: FEMALE

Animal ID	ALT IU/L	SDH IU/L	TP g/dL	ALB g/dL	GLOB g/dL	TBA umol/L	ALKP IU/L	CHOL mg/dL
GROUP: 1-F:VEHICLE (1.67 ml/kg/day)**								
311	51	8.4	7.6	4.0	3.6	14.9	231	71
312	47	14.9	8.0	4.4	3.6	15.0	281	60
313	54	15.9	6.9	3.7	3.2	17.4	191	62
314	64	11.9	8.5	4.7	3.8	37.0	258	75
315	54	12.6	7.8	4.3	3.5	24.3	194	72
316	63	17.8	7.4	4.0	3.4	52.3	229	60
317	62	12.2	7.8	4.0	3.8	21.2	247	60
318	54	12.9	7.2	3.9	3.3	37.5	246	60
319	52	9.4	6.9	4.5	2.4	20.6	251	79
320	76	9.8	8.0	4.1	3.9	14.8	207	60
MEAN	58	12.6	7.6	4.2	3.5	25.5	234	66
SD	8.5	2.98	0.52	0.31	0.43	12.65	29.1	7.5
N	10	10	10	10	10	10	10	10
GROUP: 2-F:WR279396 (0.07 ml/kg/day)**								
331	52	15.9	8.2	4.5	3.7	23.9	185	57
332	32	12.3	9.0	4.0	5.0	18.6	19	61
333	42	10.2	7.1	4.0	3.1	10.0	160	56
334	48	20.3	7.6	4.2	3.4	19.6	242	57
335	52	15.0	7.6	4.3	3.3	24.9	406	58
336	55	10.4	7.7	4.6	3.1	19.8	335	68
337	48	18.6	8.5	4.7	3.8	17.9	277	80
338	60	5.3	7.8	4.5	3.3	21.5	319	48
339	63	12.9	7.8	4.5	3.3	20.1	260	72
340	53	12.6	7.7	4.3	3.4	14.1	181	65
MEAN	51	13.4	7.9	4.4	3.5	19.0	238	62
SD	8.8	4.35	0.54	0.24	0.56	4.39	108.7	9.2
N	10	10	10	10	10	10	10	10

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD® RATS

IND. ANIMAL CLINICAL CHEMISTRY REPORT BY GROUP
PERIOD: DAY27/28

STUDY ID: UIC-12A
STUDY NO: 176
SEX: FEMALE

Animal ID	ALT IU/L	SDH IU/L	TP g/dL	ALB g/dL	GLOB g/dL	TBA umol/L	ALKP IU/L	CHOL mg/dL
GROUP: 3-F:WR279396 (0.33 ml/kg/day)**								
351	52	13.9	8.0	4.7	3.3	19.4	261	66
352	51	20.5	7.5	4.2	3.3	12.5	357	59
353	65	16.7	9.1	5.2	3.9	13.1	193	81
354	47	13.9	7.9	4.7	3.2	15.3	161	53
355	56	13.4	8.2	4.7	3.5	19.3	130	62
356	56	18.6	7.7	4.5	3.2	18.1	368	69
357	47	10.4	8.4	4.7	3.7	17.8	257	69
358	90	21.0	7.5	4.2	3.3	18.0	217	59
359	64	20.3	7.8	4.4	3.4	18.8	229	54
360	54	17.4	8.0	4.6	3.4	14.6	217	71
MEAN	58	16.6	8.0	4.6	3.4	16.7	239	64
SD	12.7	3.59	0.48	0.29	0.23	2.59	76.4	8.6
N	10	10	10	10	10	10	10	10
GROUP: 4-F:WR279396 (1.67 ml/kg/day)**								
371	51	4.3	8.7	4.7	4.0	24.5	181	89
372	49	14.7	7.3	4.1	3.2	19.2	325	57
373	100	13.7	8.2	4.8	3.4	23.8	242	75
374	48	8.7	8.4	4.5	3.9	19.3	298	88
375	63	11.3	7.4	4.0	3.4	27.2	286	73
376	45	0.1	7.3	4.2	3.1	19.4	409	63
377	43	10.6	7.7	4.3	3.4	21.7	289	69
378	50	10.0	8.6	4.4	4.2	13.5	369	77
379	46	11.1	8.3	4.5	3.8	17.3	305	77
380	61	14.0	7.3	4.1	3.2	27.7	189	56
MEAN	56	9.9	7.9	4.4	3.6	21.4	289	72
SD	16.9	4.56	0.58	0.27	0.38	4.49	71.7	11.4
N	10	10	10	10	10	10	10	10

**On days 0 -- 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD® RATS

IND. ANIMAL CLINICAL CHEMISTRY REPORT BY GROUP
PERIOD: DAY27/28

STUDY ID: UIC-12A
STUDY NO: 176
SEX: FEMALE

Animal ID	BUN mg/dL	CREAT mg/dL	NA mEq/L	K mEq/L	CL mEq/L	CA mg/dL	IP mg/dL	GLU mg/dL
GROUP: 1-F:VEHICLE (1.67 ml/kg/day)**								
311	15.5	0.57	143	6.20	108	10.0	7.8	128
312	18.4	0.54	143	6.48	104	10.8	9.1	188
313	21.1	0.60	139	5.98	107	9.3	8.6	135
314	17.0	0.53	146	5.53	107	10.7	8.9	143
315	19.5	0.57	142	4.90	106	11.1	8.5	144
316	12.5	0.49	144	5.24	103	10.9	7.1	149
317	14.7	0.65	143	5.34	102	10.3	8.0	135
318	14.9	0.52	140	5.42	99	10.2	8.0	142
319	17.4	0.57	144	5.58	108	10.6	7.0	159
320	17.4	0.58	142	5.42	110	10.9	9.3	136
MEAN	16.8	0.56	143	5.61	105	10.5	8.2	146
SD	2.52	0.045	2.0	0.476	3.3	0.54	0.79	17.1
N	10	10	10	10	10	10	10	10
GROUP: 2-F:WR279396 (0.07 ml/kg/day)**								
331	16.8	0.60	142	6.13	104	11.3	9.8	197
332	17.1	0.11	145	6.24	109	9.7	7.2	168
333	16.1	0.52	141	5.12	104	10.1	7.2	131
334	17.0	0.63	143	5.32	113	10.6	8.6	169
335	16.2	0.55	145	7.22	99	10.2	9.2	147
336	12.7	0.56	145	5.55	112	10.8	8.9	151
337	16.4	0.61	145	5.42	106	10.8	8.7	161
338	20.1	0.58	142	5.70	117	11.0	10.7	177
339	20.3	0.61	141	5.01	112	11.3	9.9	168
340	18.2	0.57	144	4.63	114	10.3	8.1	159
MEAN	17.1	0.53	143	5.63	109	10.6	8.8	163
SD	2.17	0.153	1.7	0.741	5.6	0.53	1.14	17.9
N	10	10	10	10	10	10	10	10

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD® RATS

IND. ANIMAL CLINICAL CHEMISTRY REPORT BY GROUP
PERIOD: DAY27/28

STUDY ID: UIC-12A
STUDY NO: 176
SEX: FEMALE

Animal ID	BUN mg/dL	CREAT mg/dL	NA mEq/L	K mEq/L	CL mEq/L	CA mg/dL	IP mg/dL	GLU mg/dL
GROUP: 3-F:WR279396 (0.33 ml/kg/day)**								
351	19.0	0.56	143	5.22	106	11.7	7.8	142
352	15.5	0.57	143	5.57	102	10.1	6.3	150
353	19.0	0.66	141	5.28	108	11.7	8.6	150
354	16.6	0.58	143	5.05	109	10.3	7.3	137
355	14.6	0.52	144	5.47	110	10.6	8.3	155
356	15.6	0.54	143	5.57	112	11.2	9.3	135
357	18.9	0.56	146	5.98	102	10.3	8.2	134
358	16.7	0.77	144	4.44	113	11.4	9.6	253
359	18.2	0.61	145	5.67	106	11.2	9.6	135
360	20.6	0.60	140	5.85	105	11.0	10.1	161
MEAN	17.5	0.60	143	5.41	107	11.0	8.5	155
SD	1.94	0.072	1.8	0.443	3.8	0.59	1.18	35.6
N	10	10	10	10	10	10	10	10
GROUP: 4-F:WR279396 (1.67 ml/kg/day)**								
371	16.5	0.54	141	6.01	106	10.2	7.5	159
372	14.6	0.57	143	4.80	109	10.5	7.1	164
373	16.8	0.51	145	5.13	107	11.4	9.5	137
374	18.0	0.54	146	5.60	106	11.3	8.1	129
375	16.7	0.61	144	5.46	105	11.4	8.5	173
376	16.0	0.52	143	6.15	103	10.0	6.1	139
377	15.1	0.52	146	5.54	99	10.4	8.1	151
378	15.5	0.59	143	6.24	103	11.2	9.5	148
379	14.0	0.46	145	5.54	104	10.8	7.9	138
380	17.2	0.61	142	5.30	106	10.4	7.0	195
MEAN	16.0	0.55	144	5.58	105	10.8	7.9	153
SD	1.24	0.048	1.7	0.454	2.7	0.53	1.08	20.0
N	10	10	10	10	10	10	10	10

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

APPENDIX 6

INDIVIDUAL HEMATOLOGY DATA

Hematology Test Directory

STUDY: UIC-12A

NO.	ABBR. UNITS	DESCRIPTION PRECISION	CALCULATED	OPERAND A	OPERAND B	---LOWER LIMIT--- MALE	FEMALE	---UPPER LIMIT--- MALE	FEMALE
1.	RBC 10^6/mm^3	Erythrocytes 0.00	NO			6.50	6.50	9.00	9.00
2.	HGB g/dL	Hemoglobin 0.0	NO			13.0	13.0	17.0	17.0
3.	HCT %	Hematocrit 0.0	NO			40.0	40.0	50.0	50.0
4.	MCV fL	Mean Corpuscular Volume 0.0	NO			50.0	50.0	65.0	65.0
5.	MCH pg	Mean Corpuscular Hemoglobin 0.0	NO			18.0	18.0	23.0	23.0
6.	MCHC g/dL	Mean Corpus. Hemo. Conc. 0.0	NO			32.0	32.0	39.0	39.0
7.	RETICS % RBCs	Reticulocytes 0.0	NO			0.0	0.0	1.0	1.0
8.	PLT 10^3/mm^3	Platelets Integer	NO			800	800	1400	1400
9.	WBC 10^3/mm^3	Leukocytes 0.0	NO			9.0	6.0	18.0	15.0

(END OF REPORT)

08-JUN-1995

FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD® RATS

INDIVIDUAL ANIMAL HEMATOLOGY REPORT BY GROUP
PERIOD: DAY27/28

STUDY ID: UIC-12A
STUDY NO: 176
SEX: MALE

Animal ID	RBC 10^6/mm^3	HGB g/dL	HCT %	MCV fL	MCH pg	MCHC g/dL	RETICS % RBCs	PLT 10^3/mm^3
GROUP: 1-M:VEHICLE (1.67 ml/kg/day)**								
301	7.52	15.5	42.2	56.1	20.6	36.7	0.1	952
302	7.76	16.2	43.2	55.7	20.9	37.5	0.2	1026
303	7.52	16.6	45.0	59.8	22.1	36.9	0.1	931
304	7.40	15.1	40.8	55.1	20.4	37.0	0.1	1293
305	8.04	16.4	45.1	56.1	20.4	36.4	0.1	985
306	7.41	16.0	43.9	59.2	21.6	36.4	0.1	848
307	7.42	15.9	43.4	58.5	21.4	36.6	0.0	911
308	7.80	16.1	44.3	56.8	20.6	36.3	0.3	837
309	7.78	15.4	42.1	54.1	19.8	36.6	0.0	870
310	7.33	14.9	40.9	55.8	20.3	36.4	0.0	1128
MEAN	7.60	15.8	43.1	56.7	20.8	36.7	0.1	978
SD	0.232	0.56	1.55	1.85	0.70	0.37	0.09	141.4
N	10	10	10	10	10	10	10	10
GROUP: 2-M:WR279396 (0.07 ml/kg/day)**								
321	7.71	16.1	44.7	58.0	20.9	36.0	0.1	1033
322	7.54	16.2	44.4	58.9	21.5	36.5	0.2	991
323	7.47	15.3	41.8	56.0	20.5	36.6	0.3	828
324	7.57	15.5	42.9	56.7	20.5	36.1	0.0	1041
325	7.78	16.3	45.7	58.7	21.0	35.7	0.0	1011
326	8.26	16.0	43.8	53.0	19.4	36.5	0.0	1249
327	7.68	16.1	44.3	57.7	21.0	36.3	0.2	969
328	7.91	16.3	45.1	57.0	20.6	36.1	0.1	1086
329	7.65	14.9	41.4	54.1	19.5	36.0	0.4	1195
330	--	--	--	--	--	--	--	--
MEAN	7.73	15.9	43.8	56.7	20.5	36.2	0.1	1045
SD	0.238	0.50	1.47	2.02	0.69	0.30	0.14	123.9
N	9	9	9	9	9	9	9	9

(--) - Data Unavailable

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD® RATS

INDIVIDUAL ANIMAL HEMATOLOGY REPORT BY GROUP
PERIOD: DAY27/28

STUDY ID: UIC-12A
STUDY NO: 176

SEX: MALE

Animal ID	RBC 10^6/mm^3	HGB g/dL	HCT %	MCV fL	MCH pg	MCHC g/dL	RETICS % RBCs	PLT 10^3/mm^3
GROUP: 3-M:WR279396 (0.33 ml/kg/day)**								
341	7.14	15.1	41.6	58.3	21.1	36.3	0.1	1083
342	7.95	16.2	46.5	58.5	20.4	34.8	0.3	880
343	7.95	16.4	44.7	56.2	20.6	36.7	0.1	983
344	7.61	15.9	44.0	57.8	20.9	36.1	0.0	1144
345	7.55	15.6	41.5	55.0	20.7	37.6	0.2	1027
346	8.41	16.3	45.7	54.3	19.4	35.7	0.0	904
347	7.44	15.9	46.3	62.2	21.4	34.3	0.1	1069
348	7.11	15.2	42.9	60.3	21.4	35.4	0.1	890
349	7.18	15.7	42.4	59.1	21.9	37.0	0.2	1026
350	7.36	16.0	43.1	58.6	21.7	37.1	0.0	1057
MEAN	7.57	15.8	43.9	58.0	21.0	36.1	0.1	1006
SD	0.422	0.44	1.87	2.38	0.73	1.06	0.10	89.8
N	10	10	10	10	10	10	10	10
GROUP: 4-M:WR279396 (1.67 ml/kg/day)**								
361	7.45	16.0	43.9	58.9	21.5	36.4	0.0	1034
362	8.46	17.5	48.6	57.4	20.7	36.0	0.2	768
363	7.36	16.3	45.6	62.0	22.1	35.7	0.0	899
364	7.44	16.2	44.2	59.4	21.8	36.7	0.1	953
365	7.71	14.8	41.2	53.4	19.2	35.9	0.1	918
366	8.02	17.3	47.6	59.4	21.6	36.3	0.1	838
367	7.72	16.2	44.2	57.3	21.0	36.7	0.1	872
368	7.95	16.6	45.9	57.7	20.9	36.2	0.2	952
369	6.92	16.2	43.9	63.4	23.4	36.9	0.5	1092
370	7.72	16.3	44.4	57.5	21.1	36.7	0.3	897
MEAN	7.68	16.3	45.0	58.6	21.3	36.4	0.2	922
SD	0.420	0.74	2.09	2.75	1.08	0.40	0.15	92.9
N	10	10	10	10	10	10	10	10

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

RBC MORPHOLOGY OBSERVATIONS

STUDY ID: UIC-12A
STUDY NO: 176
SEX: MALE
GROUP: 1-M : VEHICLE (1.67 ml/kg/day)**

Animal ID	DAY27/28
301	Normal Red Blood Cells
302	Normal Red Blood Cells
303	Normal Red Blood Cells
304	Normal Red Blood Cells
305	Normal Red Blood Cells
306	Normal Red Blood Cells
307	Normal Red Blood Cells
308	Normal Red Blood Cells
309	Normal Red Blood Cells
310	Normal Red Blood Cells

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

RBC MORPHOLOGY OBSERVATIONS

STUDY ID: UIC-12A
STUDY NO: 176
SEX: MALE
GROUP: 2-M : WR279396 (0.07 ml/kg/day)**

Animal ID	DAY27/28
321	Normal Red Blood Cells
322	Normal Red Blood Cells
323	Normal Red Blood Cells
324	Normal Red Blood Cells
325	Normal Red Blood Cells
326	Normal Red Blood Cells
327	Normal Red Blood Cells
328	Normal Red Blood Cells
329	Normal Red Blood Cells
330	--

(--) - Data Unavailable

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

RBC MORPHOLOGY OBSERVATIONS

STUDY ID: UIC-12A
STUDY NO: 176

SEX: MALE

GROUP: 3-M : WR279396 (0.33 ml/kg/day)**

Animal ID	DAY27/28
341	Normal Red Blood Cells
342	Normal Red Blood Cells
343	Normal Red Blood Cells
344	Normal Red Blood Cells
345	Normal Red Blood Cells
346	Normal Red Blood Cells
347	Normal Red Blood Cells
348	Normal Red Blood Cells
349	Normal Red Blood Cells
350	Normal Red Blood Cells

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

RBC MORPHOLOGY OBSERVATIONS

STUDY ID: UIC-12A
STUDY NO: 176
SEX: MALE
GROUP: 4-M : WR279396 (1.67 ml/kg/day)**

Animal ID	DAY27/28
361	Normal Red Blood Cells
362	Normal Red Blood Cells
363	Normal Red Blood Cells
364	Normal Red Blood Cells
365	Normal Red Blood Cells
366	Normal Red Blood Cells
367	Normal Red Blood Cells
368	Normal Red Blood Cells
369	Normal Red Blood Cells
370	Normal Red Blood Cells

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD® RATS

WHITE DIFFERENTIAL DATA

STUDY ID: UIC-12A
STUDY NO: 176 GROUP: 1-M : VEHICLE (1.67 ml/kg/day)** SEX: MALE

Animal ID		DAY27/28 CNT	ABS
301	Nucleated Red Cells	0	
	M. Neutrophils	11	1.9
	I. Neutrophils	0	0.0
	Lymphocytes	87	14.9
	Monocytes	2	0.3
	Eosinophils	0	0.0
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		17.1
302	Nucleated Red Cells	0	
	M. Neutrophils	8	1.3
	I. Neutrophils	0	0.0
	Lymphocytes	89	14.2
	Monocytes	3	0.5
	Eosinophils	0	0.0
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		15.9
303	Nucleated Red Cells	0	
	M. Neutrophils	21	2.8
	I. Neutrophils	0	0.0
	Lymphocytes	73	9.8
	Monocytes	6	0.8
	Eosinophils	0	0.0
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		13.4
304	Nucleated Red Cells	0	
	M. Neutrophils	5	1.0
	I. Neutrophils	0	0.0
	Lymphocytes	93	18.6
	Monocytes	2	0.4
	Eosinophils	0	0.0
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		20.0

WBC corrected for NRBC = or > 10

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD® RATS

WHITE DIFFERENTIAL DATA

STUDY ID: UIC-12A
STUDY NO: 176 GROUP: 1-M : VEHICLE (1.67 ml/kg/day)** SEX: MALE

Animal ID		DAY27/28 CNT	ABS
305	Nucleated Red Cells	0	
	M. Neutrophils	10	1.8
	I. Neutrophils	0	0.0
	Lymphocytes	88	16.0
	Monocytes	2	0.4
	Eosinophils	0	0.0
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		18.2
306	Nucleated Red Cells	0	
	M. Neutrophils	6	1.1
	I. Neutrophils	1	0.2
	Lymphocytes	87	15.3
	Monocytes	4	0.7
	Eosinophils	2	0.4
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		17.6
307	Nucleated Red Cells	0	
	M. Neutrophils	6	1.0
	I. Neutrophils	1	0.2
	Lymphocytes	92	15.3
	Monocytes	0	0.0
	Eosinophils	1	0.2
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		16.6
308	Nucleated Red Cells	0	
	M. Neutrophils	25	5.0
	I. Neutrophils	0	0.0
	Lymphocytes	72	14.3
	Monocytes	3	0.6
	Eosinophils	0	0.0
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		19.8

WBC corrected for NRBC = or > 10

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FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD® RATS

WHITE DIFFERENTIAL DATA

STUDY ID: UIC-12A
STUDY NO: 176

GROUP: 1-M : VEHICLE (1.67 ml/kg/day)**

SEX: MALE

Animal ID		DAY27/28 CNT	ABS
309	Nucleated Red Cells	0	
	M. Neutrophils	10	1.4
	I. Neutrophils	0	0.0
	Lymphocytes	88	12.1
	Monocytes	2	0.3
	Eosinophils	0	0.0
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		13.8
310	Nucleated Red Cells	0	
	M. Neutrophils	10	2.1
	I. Neutrophils	0	0.0
	Lymphocytes	87	18.4
	Monocytes	1	0.2
	Eosinophils	2	0.4
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		21.2

WBC corrected for NRBC = or > 10

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD® RATS

WHITE DIFFERENTIAL DATA

STUDY ID: UIC-12A
STUDY NO: 176

GROUP: 2-M : WR279396 (0.07 ml/kg/day)**

SEX: MALE

Animal ID		DAY27/28 CNT	ABS
321	Nucleated Red Cells	0	
	M. Neutrophils	16	3.5
	I. Neutrophils	0	0.0
	Lymphocytes	81	17.5
	Monocytes	2	0.4
	Eosinophils	1	0.2
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		21.6
322	Nucleated Red Cells	0	
	M. Neutrophils	8	1.6
	I. Neutrophils	0	0.0
	Lymphocytes	86	16.9
	Monocytes	5	1.0
	Eosinophils	1	0.2
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		19.6
323	Nucleated Red Cells	0	
	M. Neutrophils	14	2.2
	I. Neutrophils	0	0.0
	Lymphocytes	84	13.0
	Monocytes	2	0.3
	Eosinophils	0	0.0
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		15.5
324	Nucleated Red Cells	0	
	M. Neutrophils	16	2.2
	I. Neutrophils	1	0.1
	Lymphocytes	79	11.1
	Monocytes	4	0.6
	Eosinophils	0	0.0
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		14.0

WBC corrected for NRBC = or > 10

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD® RATS

WHITE DIFFERENTIAL DATA

STUOY ID: UIC-12A
STUDY NO: 176 GROUP: 2-M : WR279396 (0.07 ml/kg/day)** SEX: MALE

Animal ID		DAY27/28 CNT	ABS
325	Nucleated Red Cells	0	
	M. Neutrophils	15	2.7
	I. Neutrophils	0	0.0
	Lymphocytes	81	14.4
	Monocytes	3	0.5
	Eosinophils	1	0.2
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		17.8
326	Nucleated Red Cells	0	
	M. Neutrophils	2	0.4
	I. Neutrophils	0	0.0
	Lymphocytes	96	17.7
	Monocytes	2	0.4
	Eosinophils	0	0.0
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		18.4
327	Nucleated Red Cells	0	
	M. Neutrophils	22	4.4
	I. Neutrophils	0	0.0
	Lymphocytes	74	14.9
	Monocytes	4	0.8
	Eosinophils	0	0.0
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		20.2
328	Nucleated Red Cells	0	
	M. Neutrophils	6	1.1
	I. Neutrophils	0	0.0
	Lymphocytes	90	16.9
	Monocytes	3	0.6
	Eosinophils	1	0.2
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		18.8

WBC corrected for NRBC = or > 10

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD® RATS

WHITE DIFFERENTIAL DATA

STUDY ID: UIC-12A
STUDY NO: 176 GROUP: 2-M : WR279396 (0.07 ml/kg/day)** SEX: MALE

Animal ID		DAY27/28 CNT	ABS
329	Nucleated Red Cells	0	
	M. Neutrophils	10	1.8
	I. Neutrophils	0	0.0
	Lymphocytes	90	16.3
	Monocytes	0	0.0
	Eosinophils	0	0.0
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		18.1
330	Nucleated Red Cells	0	
	M. Neutrophils	0	--
	I. Neutrophils	0	--
	Lymphocytes	0	--
	Monocytes	0	--
	Eosinophils	0	--
	Basophils	0	--
	Atypical Lymphocytes	0	--
	WBC		--

WBC corrected for NRBC = or > 10 (--) - Data Unavailable

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

WHITE DIFFERENTIAL DATA

STUDY ID: UIC-12A
STUDY NO: 176 GROUP: 3-M : WR279396 (0.33 ml/kg/day)** SEX: MALE

Animal ID		DAY27/28 CNT	ABS
341	Nucleated Red Cells	0	
	M. Neutrophils	5	1.2
	I. Neutrophils	0	0.0
	Lymphocytes	90	21.9
	Monocytes	3	0.7
	Eosinophils	2	0.5
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		24.3
342	Nucleated Red Cells	0	
	M. Neutrophils	8	1.4
	I. Neutrophils	0	0.0
	Lymphocytes	89	15.2
	Monocytes	2	0.3
	Eosinophils	1	0.2
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		17.1
343	Nucleated Red Cells	0	
	M. Neutrophils	15	3.0
	I. Neutrophils	0	0.0
	Lymphocytes	82	16.6
	Monocytes	1	0.2
	Eosinophils	2	0.4
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		20.2
344	Nucleated Red Cells	0	
	M. Neutrophils	11	1.9
	I. Neutrophils	0	0.0
	Lymphocytes	86	14.8
	Monocytes	3	0.5
	Eosinophils	0	0.0
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		17.2

WBC corrected for NRBC = or > 10

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

WHITE DIFFERENTIAL DATA

STUDY ID: UIC-12A
STUDY NO: 176 GROUP: 3-M : WR279396 (0.33 ml/kg/day)** SEX: MALE

Animal ID		DAY27/28 CNT	ABS
345	Nucleated Red Cells	0	
	M. Neutrophils	11	1.3
	I. Neutrophils	0	0.0
	Lymphocytes	87	10.2
	Monocytes	1	0.1
	Eosinophils	1	0.1
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		11.7
346	Nucleated Red Cells	0	
	M. Neutrophils	14	2.1
	I. Neutrophils	0	0.0
	Lymphocytes	84	12.7
	Monocytes	2	0.3
	Eosinophils	0	0.0
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		15.1
347	Nucleated Red Cells	0	
	M. Neutrophils	7	1.7
	I. Neutrophils	0	0.0
	Lymphocytes	93	22.5
	Monocytes	0	0.0
	Eosinophils	0	0.0
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		24.2
348	Nucleated Red Cells	0	
	M. Neutrophils	21	3.1
	I. Neutrophils	2	0.3
	Lymphocytes	71	10.4
	Monocytes	5	0.7
	Eosinophils	1	0.1
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		14.7

WBC corrected for NRBC = or > 10

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD® RATS

WHITE DIFFERENTIAL DATA

STUDY ID: UIC-12A
STUDY NO: 176 GROUP: 3-M : WR279396 (0.33 ml/kg/day)** SEX: MALE

Animal ID		DAY27/28 CNT	ABS
349	Nucleated Red Cells	0	
	M. Neutrophils	10	1.4
	I. Neutrophils	0	0.0
	Lymphocytes	86	12.2
	Monocytes	3	0.4
	Eosinophils	1	0.1
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		14.2
350	Nucleated Red Cells	0	
	M. Neutrophils	10	1.9
	I. Neutrophils	0	0.0
	Lymphocytes	86	15.9
	Monocytes	1	0.2
	Eosinophils	3	0.6
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		18.5

WBC corrected for NRBC = or > 10

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD® RATS

WHITE DIFFERENTIAL DATA

STUDY ID: UIC-12A
STUDY NO: 176 GROUP: 4-M : WR279396 (1.67 ml/kg/day)** SEX: MALE

Animal ID		DAY27/28 CNT	ABS
361	Nucleated Red Cells	0	
	M. Neutrophils	8	1.5
	I. Neutrophils	1	0.2
	Lymphocytes	87	16.4
	Monocytes	3	0.6
	Eosinophils	1	0.2
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		18.8
362	Nucleated Red Cells	0	
	M. Neutrophils	6	1.0
	I. Neutrophils	0	0.0
	Lymphocytes	93	14.8
	Monocytes	1	0.2
	Eosinophils	0	0.0
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		15.9
363	Nucleated Red Cells	0	
	M. Neutrophils	6	1.1
	I. Neutrophils	0	0.0
	Lymphocytes	90	16.0
	Monocytes	4	0.7
	Eosinophils	0	0.0
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		17.8
364	Nucleated Red Cells	0	
	M. Neutrophils	6	2.0
	I. Neutrophils	0	0.0
	Lymphocytes	93	30.3
	Monocytes	1	0.3
	Eosinophils	0	0.0
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		32.6

WBC corrected for NRBC = or > 10

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD® RATS

WHITE DIFFERENTIAL DATA

STUDY ID: UIC-12A
STUDY NO: 176 GROUP: 4-M : WR279396 (1.67 ml/kg/day)** SEX: MALE

Animal ID		DAY27/28 CNT	ABS
365	Nucleated Red Cells	0	
	M. Neutrophils	15	2.0
	I. Neutrophils	0	0.0
	Lymphocytes	81	11.0
	Monocytes	4	0.5
	Eosinophils	0	0.0
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		13.6
366	Nucleated Red Cells	0	
	M. Neutrophils	9	1.2
	I. Neutrophils	1	0.1
	Lymphocytes	88	12.1
	Monocytes	2	0.3
	Eosinophils	0	0.0
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		13.7
367	Nucleated Red Cells	0	
	M. Neutrophils	33	6.8
	I. Neutrophils	1	0.2
	Lymphocytes	63	13.0
	Monocytes	3	0.6
	Eosinophils	0	0.0
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		20.7
368	Nucleated Red Cells	0	
	M. Neutrophils	10	1.8
	I. Neutrophils	0	0.0
	Lymphocytes	88	16.0
	Monocytes	2	0.4
	Eosinophils	0	0.0
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		18.2

WBC corrected for NRBC = or > 10

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD® RATS

WHITE DIFFERENTIAL DATA

STUDY ID: UIC-12A
STUDY NO: 176 GROUP: 4-M : WR279396 (1.67 ml/kg/day)** SEX: MALE

Animal ID		DAY27/28 CNT	ABS
369	Nucleated Red Cells	0	
	M. Neutrophils	3	0.4
	I. Neutrophils	0	0.0
	Lymphocytes	93	13.2
	Monocytes	4	0.6
	Eosinophils	0	0.0
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		14.2
370	Nucleated Red Cells	0	
	M. Neutrophils	5	1.2
	I. Neutrophils	0	0.0
	Lymphocytes	94	23.4
	Monocytes	1	0.2
	Eosinophils	0	0.0
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		24.9

WBC corrected for NRBC = or > 10

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD® RATS

INDIVIDUAL ANIMAL HEMATOLOGY REPORT BY GROUP
PERIOD: DAY27/28

STUDY ID: UIC-12A
STUDY NO: 176
SEX: FEMALE

Animal ID	RBC 10^6/mm^3	HGB g/dL	HCT %	MCV fL	MCH pg	MCHC g/dL	RETICS % RBCs	PLT 10^3/mm^3
GROUP: 1-F:VEHICLE (1.67 ml/kg/day)**								
311	6.70	14.7	39.2	58.5	21.9	37.5	0.2	1379
312	6.85	15.1	40.9	59.7	22.0	36.9	0.0	1182
313	6.94	14.9	39.5	56.9	21.5	37.7	0.1	1121
314	6.82	14.8	40.2	58.9	21.7	36.8	0.1	970
315	7.12	15.5	40.7	57.2	21.8	38.1	0.2	1161
316	7.36	15.7	42.5	57.7	21.3	36.9	0.3	978
317	7.35	16.1	42.9	58.4	21.9	37.5	0.0	1047
318	7.49	15.9	42.1	56.2	21.2	37.8	0.0	1160
319	7.69	15.9	44.8	58.3	20.7	35.5	0.4	1014
320	7.36	15.3	41.7	56.7	20.8	36.7	0.2	1134
MEAN	7.17	15.4	41.5	57.9	21.5	37.1	0.2	1115
SD	0.330	0.50	1.71	1.10	0.47	0.75	0.14	121.7
N	10	10	10	10	10	10	10	10
GROUP: 2-F:WR279396 (0.07 ml/kg/day)**								
331	7.02	15.8	42.2	60.1	22.5	37.4	0.2	1092
332	7.26	15.3	41.5	57.2	21.1	36.9	0.3	1274
333	7.08	15.2	39.7	56.1	21.5	38.3	0.2	1060
334	7.28	16.5	43.9	60.3	22.7	37.6	0.0	1090
335	7.44	16.0	42.6	57.3	21.5	37.6	0.2	931
336	7.02	15.5	40.8	58.1	22.1	38.0	0.1	1107
337	6.69	14.8	40.5	60.5	22.1	36.5	0.0	1100
338	6.55	14.4	38.6	58.9	22.0	37.3	0.3	752
339	7.13	15.0	40.2	56.4	21.0	37.3	0.8	931
340	8.22	18.1	47.6	57.9	22.0	38.0	0.0	838
MEAN	7.17	15.7	41.8	58.3	21.9	37.5	0.2	1018
SD	0.455	1.05	2.56	1.61	0.56	0.54	0.24	153.1
N	10	10	10	10	10	10	10	10

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INDIVIDUAL ANIMAL HEMATOLOGY REPORT BY GROUP
PERIOD: DAY27/28

STUDY ID: UIC-12A
STUDY NO: 176
SEX: FEMALE

Animal ID	RBC 10^6/mm^3	HGB g/dL	HCT %	MCV fL	MCH pg	MCHC g/dL	RETICS % RBCs	PLT 10^3/mm^3
GROUP: 3-F:WR279396 (0.33 ml/kg/day)**								
351	7.21	15.7	43.1	59.8	21.8	36.4	0.2	914
352	7.18	15.5	41.5	57.8	21.6	37.3	0.4	863
353	7.57	16.2	43.5	57.5	21.4	37.2	0.2	885
354	7.32	15.5	41.1	56.1	21.2	37.7	0.3	830
355	7.35	14.9	40.5	55.1	20.3	36.8	0.3	898
356	7.19	16.3	42.3	58.8	22.7	38.5	0.1	1120
357	7.09	15.1	41.2	58.1	21.3	36.7	0.2	1210
358	7.16	16.0	41.4	57.8	22.3	38.6	0.2	1111
359	7.41	15.7	42.4	57.2	21.2	37.0	0.0	1064
360	6.69	14.8	39.0	58.3	22.1	37.9	0.1	967
MEAN	7.22	15.6	41.6	57.7	21.6	37.4	0.2	986
SD	0.233	0.52	1.31	1.32	0.68	0.75	0.12	130.3
N	10	10	10	10	10	10	10	10
GROUP: 4-F:WR279396 (1.67 ml/kg/day)**								
371	7.89	16.4	43.6	55.3	20.8	37.6	0.3	1300
372	6.62	14.5	37.9	57.3	21.9	38.3	0.0	1112
373	6.76	14.3	38.1	56.4	21.2	37.5	0.1	1111
374	7.21	15.2	41.2	57.1	21.1	36.9	0.0	1109
375	7.77	16.5	45.3	58.3	21.2	36.4	0.4	1120
376	7.12	15.1	40.6	57.0	21.2	37.2	0.1	1090
377	6.88	15.5	40.2	58.4	22.5	38.6	0.0	1082
378	7.68	15.9	43.5	56.6	20.7	36.6	0.2	1100
379	7.00	15.1	41.2	58.9	21.6	36.7	0.3	904
380	8.18	16.8	45.9	56.1	20.5	36.6	0.2	1080
MEAN	7.31	15.5	41.8	57.1	21.3	37.2	0.2	1101
SD	0.532	0.85	2.76	1.12	0.60	0.75	0.14	94.3
N	10	10	10	10	10	10	10	10

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

RBC MORPHOLOGY OBSERVATIONS

STUDY ID: UIC-12A
STUDY NO: 176
SEX: FEMALE
GROUP: 1-F : VEHICLE (1.67 ml/kg/day)**

Animal ID	DAY27/28
311	Normal Red Blood Cells
312	Normal Red Blood Cells
313	Normal Red Blood Cells
314	Normal Red Blood Cells
315	Normal Red Blood Cells
316	Normal Red Blood Cells
317	Normal Red Blood Cells
318	Normal Red Blood Cells
319	Normal Red Blood Cells
320	Normal Red Blood Cells

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD® RATS

RBC MORPHOLOGY OBSERVATIONS

STUDY ID: UIC-12A
STUDY NO: 176
GROUP: 2-F : WR279396 (0.07 ml/kg/day)**
SEX: FEMALE

Animal ID	DAY27/28
331	Normal Red Blood Cells
332	Normal Red Blood Cells
333	Normal Red Blood Cells
334	Normal Red Blood Cells
335	Normal Red Blood Cells
336	Normal Red Blood Cells
337	Normal Red Blood Cells
338	Normal Red Blood Cells
339	Normal Red Blood Cells
340	Normal Red Blood Cells

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

RBC MORPHOLOGY OBSERVATIONS

STUDY ID: UIC-12A
STUDY NO: 176
SEX: FEMALE
GROUP: 3-F : WR279396 (0.33 ml/kg/day)**

Animal ID	DAY27/28
351	Normal Red Blood Cells
352	Normal Red Blood Cells
353	Normal Red Blood Cells
354	Normal Red Blood Cells
355	Normal Red Blood Cells
356	Normal Red Blood Cells
357	Normal Red Blood Cells
358	Normal Red Blood Cells
359	Normal Red Blood Cells
360	Normal Red Blood Cells

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

RBC MORPHOLOGY OBSERVATIONS

STUDY ID: UIC-12A
STUDY NO: 176
SEX: FEMALE
GROUP: 4-F : WR279396 (1.67 ml/kg/day)**

Animal ID	DAY27/28
371	Normal Red Blood Cells
372	Normal Red Blood Cells
373	Normal Red Blood Cells
374	Normal Red Blood Cells
375	Normal Red Blood Cells
376	Normal Red Blood Cells
377	Normal Red Blood Cells
378	Normal Red Blood Cells
379	Normal Red Blood Cells
380	Normal Red Blood Cells

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

WHITE DIFFERENTIAL DATA

STUDY ID: UIC-12A
STUDY NO: 176 GROUP: 1-F : VEHICLE (1.67 ml/kg/day)** SEX: FEMALE

Animal ID		DAY27/28 CNT	ABS
311	Nucleated Red Cells	0	
	M. Neutrophils	13	2.1
	I. Neutrophils	0	0.0
	Lymphocytes	85	13.5
	Monocytes	2	0.3
	Eosinophils	0	0.0
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		15.9
312	Nucleated Red Cells	0	
	M. Neutrophils	4	0.7
	I. Neutrophils	1	0.2
	Lymphocytes	92	15.5
	Monocytes	2	0.3
	Eosinophils	1	0.2
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		16.9
313	Nucleated Red Cells	0	
	M. Neutrophils	25	3.6
	I. Neutrophils	0	0.0
	Lymphocytes	71	10.3
	Monocytes	3	0.4
	Eosinophils	1	0.1
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		14.5
314	Nucleated Red Cells	0	
	M. Neutrophils	3	0.7
	I. Neutrophils	0	0.0
	Lymphocytes	95	23.0
	Monocytes	2	0.5
	Eosinophils	0	0.0
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		24.2

WBC corrected for NRBC = or > 10

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD® RATS

WHITE DIFFERENTIAL DATA

STUDY ID: UIC-12A
STUDY NO: 176 GROUP: 1-F : VEHICLE (1.67 ml/kg/day)** SEX: FEMALE

Animal ID		DAY27/28 CNT	ABS
315	Nucleated Red Cells	0	
	M. Neutrophils	19	4.1
	I. Neutrophils	0	0.0
	Lymphocytes	77	16.8
	Monocytes	1	0.2
	Eosinophils	3	0.7
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		21.8
316	Nucleated Red Cells	0	
	M. Neutrophils	8	1.7
	I. Neutrophils	0	0.0
	Lymphocytes	91	19.3
	Monocytes	1	0.2
	Eosinophils	0	0.0
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		21.2
317	Nucleated Red Cells	0	
	M. Neutrophils	10	1.8
	I. Neutrophils	0	0.0
	Lymphocytes	86	15.3
	Monocytes	3	0.5
	Eosinophils	1	0.2
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		17.8
318	Nucleated Red Cells	0	
	M. Neutrophils	9	1.5
	I. Neutrophils	0	0.0
	Lymphocytes	89	14.5
	Monocytes	2	0.3
	Eosinophils	0	0.0
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		16.3

WBC corrected for NRBC = or > 10

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

WHITE DIFFERENTIAL DATA

STUDY ID: UIC-12A
STUDY NO: 176 GROUP: 1-F : VEHICLE (1.67 ml/kg/day)** SEX: FEMALE

Animal ID		DAY27/28 CNT	ABS
319	Nucleated Red Cells	0	
	M. Neutrophils	10	1.7
	I. Neutrophils	0	0.0
	Lymphocytes	87	15.0
	Monocytes	3	0.5
	Eosinophils	0	0.0
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		17.2
320	Nucleated Red Cells	0	
	M. Neutrophils	10	1.5
	I. Neutrophils	0	0.0
	Lymphocytes	88	13.1
	Monocytes	2	0.3
	Eosinophils	0	0.0
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		14.9

WBC corrected for NRBC = or > 10

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

WHITE DIFFERENTIAL DATA

STUDY ID: UIC-12A
STUDY NO: 176 GROUP: 2-F : WR279396 (0.07 ml/kg/day)** SEX: FEMALE

Animal ID		DAY27/28 CNT	ABS
331	Nucleated Red Cells	0	
	M. Neutrophils	11	1.6
	I. Neutrophils	0	0.0
	Lymphocytes	88	12.7
	Monocytes	1	0.1
	Eosinophils	0	0.0
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		14.4
332	Nucleated Red Cells	0	
	M. Neutrophils	5	0.9
	I. Neutrophils	0	0.0
	Lymphocytes	95	17.0
	Monocytes	0	0.0
	Eosinophils	0	0.0
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		17.9
333	Nucleated Red Cells	0	
	M. Neutrophils	6	1.2
	I. Neutrophils	0	0.0
	Lymphocytes	92	18.2
	Monocytes	1	0.2
	Eosinophils	1	0.2
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		19.8
334	Nucleated Red Cells	0	
	M. Neutrophils	25	3.8
	I. Neutrophils	2	0.3
	Lymphocytes	71	10.9
	Monocytes	1	0.2
	Eosinophils	1	0.2
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		15.3

WBC corrected for NRBC = or > 10

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD® RATS

WHITE DIFFERENTIAL DATA

STUDY ID: UIC-12A
STUDY NO: 176 GROUP: 2-F : WR279396 (0.07 ml/kg/day)** SEX: FEMALE

Animal ID		DAY27/28 CNT	ABS
335	Nucleated Red Cells	0	
	M. Neutrophils	8	1.4
	I. Neutrophils	0	0.0
	Lymphocytes	89	15.8
	Monocytes	3	0.5
	Eosinophils	0	0.0
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		17.7
336	Nucleated Red Cells	0	
	M. Neutrophils	18	2.0
	I. Neutrophils	0	0.0
	Lymphocytes	81	8.8
	Monocytes	1	0.1
	Eosinophils	0	0.0
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		10.9
337	Nucleated Red Cells	0	
	M. Neutrophils	14	2.2
	I. Neutrophils	1	0.2
	Lymphocytes	79	12.2
	Monocytes	5	0.8
	Eosinophils	1	0.2
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		15.4
338	Nucleated Red Cells	0	
	M. Neutrophils	11	1.7
	I. Neutrophils	0	0.0
	Lymphocytes	88	13.9
	Monocytes	1	0.2
	Eosinophils	0	0.0
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		15.8

WBC corrected for NRBC = or > 10

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD® RATS

WHITE DIFFERENTIAL DATA

STUDY ID: UIC-12A
STUDY NO: 176 GROUP: 2-F : WR279396 (0.07 ml/kg/day)** SEX: FEMALE

Animal ID		DAY27/28 CNT	ABS
339	Nucleated Red Cells	0	
	M. Neutrophils	10	1.3
	I. Neutrophils	0	0.0
	Lymphocytes	86	11.3
	Monocytes	3	0.4
	Eosinophils	1	0.1
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		13.1
340	Nucleated Red Cells	0	
	M. Neutrophils	0	0.0
	I. Neutrophils	0	0.0
	Lymphocytes	97	10.3
	Monocytes	2	0.2
	Eosinophils	1	0.1
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		10.6

WBC corrected for NRBC = or > 10

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

WHITE DIFFERENTIAL DATA

STUDY ID: UIC-12A
STUDY NO: 176 GROUP: 3-F : WR279396 (0.33 ml/kg/day)** SEX: FEMALE

Animal ID		DAY27/28 CNT	ABS
351	Nucleated Red Cells	0	
	M. Neutrophils	15	2.3
	I. Neutrophils	0	0.0
	Lymphocytes	83	12.6
	Monocytes	1	0.2
	Eosinophils	1	0.2
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		15.2
352	Nucleated Red Cells	0	
	M. Neutrophils	12	1.8
	I. Neutrophils	0	0.0
	Lymphocytes	84	12.5
	Monocytes	4	0.6
	Eosinophils	0	0.0
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		14.9
353	Nucleated Red Cells	0	
	M. Neutrophils	6	0.9
	I. Neutrophils	0	0.0
	Lymphocytes	92	13.2
	Monocytes	2	0.3
	Eosinophils	0	0.0
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		14.4
354	Nucleated Red Cells	0	
	M. Neutrophils	4	0.6
	I. Neutrophils	0	0.0
	Lymphocytes	94	13.1
	Monocytes	2	0.3
	Eosinophils	0	0.0
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		13.9

WBC corrected for NRBC = or > 10

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD® RATS

WHITE DIFFERENTIAL DATA

STUDY ID: UIC-12A
STUDY NO: 176 GROUP: 3-F : WR279396 (0.33 ml/kg/day)** SEX: FEMALE

Animal ID		DAY27/28 CNT	ABS
355	Nucleated Red Cells	0	
	M. Neutrophils	8	0.8
	I. Neutrophils	0	0.0
	Lymphocytes	91	9.0
	Monocytes	1	0.1
	Eosinophils	0	0.0
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		9.9
356	Nucleated Red Cells	0	
	M. Neutrophils	3	0.5
	I. Neutrophils	0	0.0
	Lymphocytes	94	16.6
	Monocytes	3	0.5
	Eosinophils	0	0.0
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		17.7
357	Nucleated Red Cells	0	
	M. Neutrophils	10	2.0
	I. Neutrophils	0	0.0
	Lymphocytes	90	17.6
	Monocytes	0	0.0
	Eosinophils	0	0.0
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		19.5
358	Nucleated Red Cells	0	
	M. Neutrophils	7	1.0
	I. Neutrophils	0	0.0
	Lymphocytes	89	13.3
	Monocytes	1	0.1
	Eosinophils	3	0.4
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		14.9

WBC corrected for NRBC = or > 10

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD® RATS

WHITE DIFFERENTIAL DATA

STUDY ID: UIC-12A
STUDY NO: 176 GROUP: 3-F : WR279396 (0.33 ml/kg/day)** SEX: FEMALE

Animal ID		DAY27/28 CNT	ABS
359	Nucleated Red Cells	0	
	M. Neutrophils	12	1.9
	I. Neutrophils	0	0.0
	Lymphocytes	87	13.5
	Monocytes	0	0.0
	Eosinophils	1	0.2
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		15.5
360	Nucleated Red Cells	0	
	M. Neutrophils	15	2.3
	I. Neutrophils	0	0.0
	Lymphocytes	83	12.6
	Monocytes	1	0.2
	Eosinophils	1	0.2
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		15.2

WBC corrected for NRBC = or > 10

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD® RATS

WHITE DIFFERENTIAL DATA

STUDY ID: UIC-12A
STUDY NO: 176 GROUP: 4-F : WR279396 (1.67 ml/kg/day)** SEX: FEMALE

Animal ID		DAY27/28 CNT	ABS
371	Nucleated Red Cells	0	
	M. Neutrophils	11	1.8
	I. Neutrophils	0	0.0
	Lymphocytes	85	13.6
	Monocytes	2	0.3
	Eosinophils	2	0.3
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		16.0
372	Nucleated Red Cells	0	
	M. Neutrophils	8	0.7
	I. Neutrophils	0	0.0
	Lymphocytes	89	8.2
	Monocytes	2	0.2
	Eosinophils	1	0.1
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		9.2
373	Nucleated Red Cells	0	
	M. Neutrophils	4	0.5
	I. Neutrophils	0	0.0
	Lymphocytes	95	12.8
	Monocytes	1	0.1
	Eosinophils	0	0.0
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		13.5
374	Nucleated Red Cells	0	
	M. Neutrophils	12	1.7
	I. Neutrophils	0	0.0
	Lymphocytes	85	12.2
	Monocytes	3	0.4
	Eosinophils	0	0.0
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		14.4

WBC corrected for NRBC = or > 10

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD® RATS

WHITE DIFFERENTIAL DATA

STUDY ID: UIC-12A
STUDY NO: 176 GROUP: 4-F : WR279396 (1.67 ml/kg/day)** SEX: FEMALE

Animal ID		DAY27/28 CNT	ABS
375	Nucleated Red Cells	0	
	M. Neutrophils	12	2.0
	I. Neutrophils	0	0.0
	Lymphocytes	87	14.4
	Monocytes	1	0.2
	Eosinophils	0	0.0
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		16.5
376	Nucleated Red Cells	0	
	M. Neutrophils	3	0.4
	I. Neutrophils	0	0.0
	Lymphocytes	96	13.6
	Monocytes	1	0.1
	Eosinophils	0	0.0
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		14.2
377	Nucleated Red Cells	0	
	M. Neutrophils	2	0.2
	I. Neutrophils	0	0.0
	Lymphocytes	95	11.2
	Monocytes	1	0.1
	Eosinophils	2	0.2
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		11.8
378	Nucleated Red Cells	0	
	M. Neutrophils	8	2.4
	I. Neutrophils	1	0.3
	Lymphocytes	88	26.7
	Monocytes	3	0.9
	Eosinophils	0	0.0
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		30.3

WBC corrected for NRBC = or > 10

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

WHITE DIFFERENTIAL DATA

STUDY ID: UIC-12A
STUDY NO: 176 GROUP: 4-F : WR279396 (1.67 ml/kg/day)** SEX: FEMALE

Animal ID		DAY27/28 CNT	ABS
379	Nucleated Red Cells	0	
	M. Neutrophils	11	1.6
	I. Neutrophils	0	0.0
	Lymphocytes	89	12.8
	Monocytes	0	0.0
	Eosinophils	0	0.0
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		14.4
380	Nucleated Red Cells	0	
	M. Neutrophils	2	0.4
	I. Neutrophils	0	0.0
	Lymphocytes	96	19.3
	Monocytes	1	0.2
	Eosinophils	1	0.2
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		20.1

WBC corrected for NRBC = or > 10

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

APPENDIX 7

OPHTHALMOLOGY REPORT

ANIMAL EYE ASSOCIATES

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May 11, 1995

OPHTHALMIC REPORT

UIC/TRL Study No. 176

FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD® RATS

During Week -1 (February 21, 1995), a sufficient number of male and female CD® rats were given ophthalmic examinations by indirect ophthalmoscopy to result in forty rats/sex which were within normal limits.

During Week 4 (March 21, 1995), seventy-nine rats which were used in the above-referenced study were re-examined (one rat died on study). One mid dose male (animal no. 350) appeared to have a zone of retinal and choroidal atrophy of its left eye. The lesion is typical of trauma to the eye (the globe) and not a test article-related effect. All other rats appeared similar (no lesions) to their pretest examination on February 21, 1995.

Sincerely,

Samuel J. Vainisi, D.V.M.
Professor of Comparative
Ophthalmology, U. of IL. at Chicago

Diplomate, American College of
Veterinary Ophthalmologists

FOUR WEEK TOXICITY STUDY OF WR279396 AFTER DAILY DERMAL APPLICATION IN CD® RATS

Ophthalmic Examinations
Males

Treatment Group	Animal Number	Week -1 R.E.	Week -1 L.E.	Week 4 R.E.	Week 4 L.E.
Vehicle 1.67 ml/kg/day[a]	301	WNL	WNL	WNL	WNL
	302	WNL	WNL	WNL	WNL
	303	WNL	WNL	WNL	WNL
	304	WNL	WNL	WNL	WNL
	305	WNL	WNL	WNL	WNL
	306	WNL	WNL	WNL	WNL
	307	WNL	WNL	WNL	WNL
	308	WNL	WNL	WNL	WNL
	309	WNL	WNL	WNL	WNL
	310	WNL	WNL	WNL	WNL
WR279396 0.07 ml/kg/day[a]	321	WNL	WNL	WNL	WNL
	322	WNL	WNL	WNL	WNL
	323	WNL	WNL	WNL	WNL
	324	WNL	WNL	WNL	WNL
	325	WNL	WNL	WNL	WNL
	326	WNL	WNL	WNL	WNL
	327	WNL	WNL	WNL	WNL
	328	WNL	WNL	WNL	WNL
	329	WNL	WNL	WNL	WNL
	330	WNL	WNL	*	*
WR279396 0.33 ml/kg/day[a]	341	WNL	WNL	WNL	WNL
	342	WNL	WNL	WNL	WNL
	343	WNL	WNL	WNL	WNL
	344	WNL	WNL	WNL	WNL
	345	WNL	WNL	WNL	WNL
	346	WNL	WNL	WNL	WNL
	347	WNL	WNL	WNL	WNL
	348	WNL	WNL	WNL	WNL
	349	WNL	WNL	WNL	WNL
	350	WNL	WNL	WNL	ZRCA
WR279396 1.67 ml/kg/day[a]	361	WNL	WNL	WNL	WNL
	362	WNL	WNL	WNL	WNL
	363	WNL	WNL	WNL	WNL
	364	WNL	WNL	WNL	WNL
	365	WNL	WNL	WNL	WNL
	366	WNL	WNL	WNL	WNL
	367	WNL	WNL	WNL	WNL
	368	WNL	WNL	WNL	WNL
	369	WNL	WNL	WNL	WNL
	370	WNL	WNL	WNL	WNL

[a]On days 0 - 5, animals were treated twice daily with the shown volume of test article or vehicle control article.

R.E. = Right Eye
L.E. = Left Eye
* = Animal Previously Died
WNL = Within Normal Limits
ZRCA = Zone of Retinal and Choroidal Atrophy

FOUR WEEK TOXICITY STUDY OF WR279396 AFTER DAILY DERMAL APPLICATION IN CD® RATS

Ophthalmic Examinations
Females

Treatment Group	Animal Number	Week -1 R.E.	Week -1 L.E.	Week 4 R.E.	Week 4 L.E.
Vehicle 1.67 ml/kg/day[a]	311	WNL	WNL	WNL	WNL
	312	WNL	WNL	WNL	WNL
	313	WNL	WNL	WNL	WNL
	314	WNL	WNL	WNL	WNL
	315	WNL	WNL	WNL	WNL
	316	WNL	WNL	WNL	WNL
	317	WNL	WNL	WNL	WNL
	318	WNL	WNL	WNL	WNL
	319	WNL	WNL	WNL	WNL
	320	WNL	WNL	WNL	WNL
WR279396 0.07 ml/kg/day[a]	331	WNL	WNL	WNL	WNL
	332	WNL	WNL	WNL	WNL
	333	WNL	WNL	WNL	WNL
	334	WNL	WNL	WNL	WNL
	335	WNL	WNL	WNL	WNL
	336	WNL	WNL	WNL	WNL
	337	WNL	WNL	WNL	WNL
	338	WNL	WNL	WNL	WNL
	339	WNL	WNL	WNL	WNL
	340	WNL	WNL	WNL	WNL
WR279396 0.33 ml/kg/day[a]	351	WNL	WNL	WNL	WNL
	352	WNL	WNL	WNL	WNL
	353	WNL	WNL	WNL	WNL
	354	WNL	WNL	WNL	WNL
	355	WNL	WNL	WNL	WNL
	356	WNL	WNL	WNL	WNL
	357	WNL	WNL	WNL	WNL
	358	WNL	WNL	WNL	WNL
	359	WNL	WNL	WNL	WNL
	360	WNL	WNL	WNL	WNL
WR279396 1.67 ml/kg/day[a]	371	WNL	WNL	WNL	WNL
	372	WNL	WNL	WNL	WNL
	373	WNL	WNL	WNL	WNL
	374	WNL	WNL	WNL	WNL
	375	WNL	WNL	WNL	WNL
	376	WNL	WNL	WNL	WNL
	377	WNL	WNL	WNL	WNL
	378	WNL	WNL	WNL	WNL
	379	WNL	WNL	WNL	WNL
	380	WNL	WNL	WNL	WNL

[a]On days 0 - 5, animals were treated twice daily with the shown volume of test article or vehicle control article.

R.E. = Right Eye
L.E. = Left Eye
* = Animal Previously Died
WNL = Within Normal Limits
ZRCA = Zone of Retinal and Choroidal Atrophy

APPENDIX 8

INDIVIDUAL ORGAN WEIGHTS

FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD® RATS

INDIVIDUAL ORGAN WEIGHTS

STUDY: 176
SEX: MALE

GROUP: 1-M - VEHICLE (1.67 ml/kg/day)**
ALL FATES DAYS: BEGINNING-29 ALL BALANCES

ANIMAL ID: / BALANCE NO.:	301	302	303	304	305	306	307	308	309
BODY WEIGHT (G)	407	432	419	422	407	470	461	415	390
Adrenal Glands (G)	0.075	0.133	0.064	0.063	0.128	0.087	0.096	0.084	0.093
% BRAIN WEIGHT	3.40	6.22	2.91	3.00	5.37	3.91	4.47	3.80	4.14
Brain (G)	2.205	2.138	2.200	2.103	2.382	2.224	2.147	2.209	2.249
Heart (G)	1.459	1.818	1.295	1.166	1.394	1.564	1.439	1.080	1.773
% BRAIN WEIGHT	66.17	85.03	58.86	55.44	58.52	70.32	67.02	48.89	78.84
Kidneys (G)	3.494	3.419	3.113	3.464	4.435	3.811	4.289	3.779	3.026
% BRAIN WEIGHT	158.46	159.92	141.50	164.72	186.19	171.36	199.77	171.07	134.55
Liver (G)	15.430	19.386	17.702	19.009	17.020	20.114	17.941	19.560	16.040
% BRAIN WEIGHT	699.77	906.74	804.64	903.90	714.53	904.41	835.63	885.47	713.21
Lung/Bronchi (G)	2.168	2.474	1.835	2.139	2.618	2.328	2.251	2.594	2.076
% BRAIN WEIGHT	98.32	115.72	83.41	101.71	109.91	104.68	104.84	117.43	92.31
Spleen (G)	0.704	0.915	0.726	0.655	0.811	0.852	0.690	0.782	0.751
% BRAIN WEIGHT	31.93	42.80	33.00	31.15	34.05	38.31	32.14	35.40	33.39
Testes (G)	3.260	3.291	3.153	3.289	3.280	2.965	3.450	3.401	3.159
% BRAIN WEIGHT	147.85	153.93	143.32	156.40	137.70	133.32	160.69	153.96	140.46

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD® RATS

INDIVIDUAL ORGAN WEIGHTS

STUDY: 176
SEX: MALE

GROUP: 1-M - VEHICLE (1.67 ml/kg/day)**
ALL FATES DAYS: BEGINNING-29 ALL BALANCES

ANIMAL ID:	310
BALANCE NO.:	
BODY WEIGHT (G)	452
Adrenal Glands (G)	0.084
% BRAIN WEIGHT	3.68
Brain (G)	2.283
Heart (G)	1.319
% BRAIN WEIGHT	57.77
Kidneys (G)	4.175
% BRAIN WEIGHT	182.87
Liver (G)	15.959
% BRAIN WEIGHT	699.04
Lung/Bronchi (G)	2.037
% BRAIN WEIGHT	89.22
Spleen (G)	1.102
% BRAIN WEIGHT	48.27
Testes (G)	3.970
% BRAIN WEIGHT	173.89

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD® RATS

INDIVIDUAL ORGAN WEIGHTS

STUDY: 176
SEX: MALE

GROUP: 2-M - WR279396 (0.07 ml/kg/day)**
ALL FATES DAYS: BEGINNING-29 ALL BALANCES

ANIMAL ID: / BALANCE NO.:	321	322	323	324	325	326	327	328	329
BODY WEIGHT (G)	425	421	431	474	405	457	405	420	421
Adrenal Glands (G)	0.065	0.107	0.082	0.095	0.069	0.072	0.068	0.079	0.063
% BRAIN WEIGHT	2.85	4.54	3.67	4.44	2.99	3.20	3.44	3.54	2.86
Brain (G)	2.280	2.359	2.235	2.142	2.309	2.252	1.974	2.233	2.203
Heart (G)	1.610	1.601	1.183	1.396	1.526	1.637	1.364	1.395	1.211
% BRAIN WEIGHT	70.61	67.87	52.93	65.17	66.09	72.69	69.10	62.47	54.97
Kidneys (G)	4.737	4.443	3.827	3.392	4.228	4.389	3.523	3.526	4.170
% BRAIN WEIGHT	207.76	188.34	171.23	158.36	183.11	194.89	178.47	157.90	189.29
Liver (G)	17.756	16.040	17.279	19.025	14.947	19.249	16.683	15.350	17.892
% BRAIN WEIGHT	778.77	679.95	773.11	888.19	647.34	854.75	845.14	687.42	812.17
Lung/Bronchi (G)	2.510	2.268	2.390	2.475	2.383	2.293	2.332	2.573	2.245
% BRAIN WEIGHT	110.09	96.14	106.94	115.55	103.20	101.82	118.14	115.23	101.91
Spleen (G)	0.840	0.845	0.886	1.006	1.056	0.756	0.705	0.729	0.903
% BRAIN WEIGHT	36.84	35.82	39.64	46.97	45.73	33.57	35.71	32.65	40.99
Testes (G)	3.326	3.170	3.564	3.510	3.332	3.085	3.543	3.270	2.975
% BRAIN WEIGHT	145.88	134.38	159.46	163.87	144.30	136.99	179.48	146.44	135.04

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD® RATS

INDIVIDUAL ORGAN WEIGHTS

STUDY: 176
SEX: MALE

GROUP: 3-M - WR279396 (0.33 ml/kg/day)**
ALL FATES DAYS: BEGINNING-29 ALL BALANCES

ANIMAL ID: / BALANCE NO.:	341	342	343	344	345	346	347	348	349
BODY WEIGHT (G)	487	437	430	432	430	381	454	446	463
Adrenal Glands (G)	0.087	0.114	0.075	0.078	0.072	0.072	0.044	0.060	0.147
% BRAIN WEIGHT	3.86	4.77	3.27	3.33	3.33	3.64	2.05	2.59	6.56
Brain (G)	2.253	2.388	2.293	2.342	2.161	1.976	2.144	2.315	2.240
Heart (G)	1.706	1.885	1.485	1.606	1.400	1.007	1.744	1.650	1.860
% BRAIN WEIGHT	75.72	78.94	64.76	68.57	64.78	50.96	81.34	71.27	83.04
Kidneys (G)	3.913	3.795	4.148	3.754	4.582	3.789	4.019	3.184	4.876
% BRAIN WEIGHT	173.68	158.92	180.90	160.29	212.03	191.75	187.45	137.54	217.68
Liver (G)	20.568	18.451	14.842	18.990	20.486	16.651	18.269	16.045	19.888
% BRAIN WEIGHT	912.92	772.65	647.27	810.85	947.99	842.66	852.10	693.09	887.86
Lung/Bronchi (G)	2.725	3.420	2.448	2.755	2.204	2.075	2.883	2.426	2.569
% BRAIN WEIGHT	120.95	143.22	106.76	117.63	101.99	105.01	134.47	104.79	114.69
Spleen (G)	0.839	0.716	0.773	0.773	0.792	0.694	0.968	0.927	0.707
% BRAIN WEIGHT	37.24	29.98	33.71	33.01	36.65	35.12	45.15	40.04	31.56
Testes (G)	3.430	3.258	3.189	3.736	3.450	2.939	3.231	3.622	3.184
% BRAIN WEIGHT	152.24	136.43	139.08	159.52	159.65	148.73	150.70	156.46	142.14

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD® RATS

INDIVIDUAL ORGAN WEIGHTS

STUDY: 176
SEX: MALE

GROUP: 3-M - WR279396 (0.33 ml/kg/day)**
ALL FATES DAYS: BEGINNING-29 ALL BALANCES

ANIMAL ID:	350
BALANCE NO.:	
BODY WEIGHT (G)	489
Adrenal Glands (G)	0.059
% BRAIN WEIGHT	2.62
Brain (G)	2.256
Heart (G)	1.585
% BRAIN WEIGHT	70.26
Kidneys (G)	3.770
% BRAIN WEIGHT	167.11
Liver (G)	19.693
% BRAIN WEIGHT	872.92
Lung/Bronchi (G)	3.479
% BRAIN WEIGHT	154.21
Spleen (G)	0.975
% BRAIN WEIGHT	43.22
Testes (G)	3.180
% BRAIN WEIGHT	140.96

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FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD® RATS

INDIVIDUAL ORGAN WEIGHTS

STUDY: 176
SEX: MALE

GROUP: 4-M - WR279396 (1.67 ml/kg/day)**
ALL FATES DAYS: BEGINNING-29 ALL BALANCES

ANIMAL ID: / BALANCE NO.:	361	362	363	364	365	366	367	368	369
BODY WEIGHT (G)	411	449	444	460	417	404	434	383	504
Adrenal Glands (G)	0.103	0.083	0.091	0.092	0.110	0.087	0.072	0.053	0.089
% BRAIN WEIGHT	4.46	4.01	4.29	4.25	4.65	4.33	3.40	2.60	4.24
Brain (G)	2.307	2.068	2.119	2.167	2.364	2.010	2.119	2.035	2.097
Heart (G)	1.300	1.511	1.271	1.399	1.530	1.193	1.461	1.592	1.581
% BRAIN WEIGHT	56.35	73.07	59.98	64.56	64.72	59.35	68.95	78.23	75.39
Kidneys (G)	4.400	3.533	2.281	4.060	4.143	3.807	3.596	3.347	4.452
% BRAIN WEIGHT	190.72	170.84	107.65	187.36	175.25	189.40	169.70	164.47	212.30
Liver (G)	16.748	20.482	16.450	17.746	16.565	16.420	15.748	16.046	21.882
% BRAIN WEIGHT	725.96	990.43	776.31	818.92	700.72	816.92	743.18	788.50	1043.49
Lung/Bronchi (G)	2.568	2.513	2.678	2.328	1.914	2.245	2.236	2.380	1.840
% BRAIN WEIGHT	111.31	121.52	126.38	107.43	80.96	111.69	105.52	116.95	87.74
Spleen (G)	0.875	0.903	0.978	1.179	0.641	0.689	0.794	0.629	0.882
% BRAIN WEIGHT	37.93	43.67	46.15	54.41	27.12	34.28	37.47	30.91	42.06
Testes (G)	3.960	3.535	3.024	3.479	3.446	2.934	2.876	3.063	4.141
% BRAIN WEIGHT	171.65	170.94	142.71	160.54	145.77	145.97	135.72	150.52	197.47

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD® RATS

INDIVIDUAL ORGAN WEIGHTS

STUDY: 176
SEX: MALE

GROUP: 4-M - WR279396 (1.67 ml/kg/day)**
ALL FATES DAYS: BEGINNING-29 ALL BALANCES

ANIMAL ID:	370
BALANCE NO.:	
BODY WEIGHT (G)	451
Adrenal Glands (G)	0.070
% BRAIN WEIGHT	3.03
Brain (G)	2.314
Heart (G)	1.320
% BRAIN WEIGHT	57.04
Kidneys (G)	3.723
% BRAIN WEIGHT	160.89
Liver (G)	16.617
% BRAIN WEIGHT	718.11
Lung/Bronchi (G)	2.764
% BRAIN WEIGHT	119.45
Spleen (G)	1.145
% BRAIN WEIGHT	49.48
Testes (G)	3.470
% BRAIN WEIGHT	149.96

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FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD® RATS

INDIVIDUAL ORGAN WEIGHTS

STUDY: 176
SEX: FEMALE
GROUP: 1-F - VEHICLE (1.67 ml/kg/day)**
ALL FATES DAYS: BEGINNING-29 ALL BALANCES

ANIMAL ID: / BALANCE NO.:	311	312	313	314	315	316	317	318	319
BODY WEIGHT (G)	290	276	293	271	286	270	253	271	274
Adrenal Glands (G)	0.073	0.106	0.078	0.086	0.088	0.142	0.095	0.088	0.042
% BRAIN WEIGHT	3.30	5.17	3.59	4.32	4.45	6.61	4.49	3.92	2.05
Brain (G)	2.211	2.049	2.175	1.989	1.977	2.148	2.118	2.244	2.050
Heart (G)	1.082	0.762	1.064	0.964	0.891	1.281	0.805	0.933	1.272
% BRAIN WEIGHT	48.94	37.19	48.92	48.47	45.07	59.64	38.01	41.58	62.05
Kidneys (G)	2.209	3.028	2.039	2.979	2.712	2.612	2.084	2.358	2.772
% BRAIN WEIGHT	99.91	147.78	93.75	149.77	137.18	121.60	98.39	105.08	135.22
Liver (G)	13.166	11.904	12.605	13.705	11.604	11.385	9.229	9.637	10.986
% BRAIN WEIGHT	595.48	580.97	579.54	689.04	586.95	530.03	435.74	429.46	535.90
Lung/Bronchi (G)	1.655	2.023	1.646	1.426	2.293	2.027	1.773	1.641	3.042
% BRAIN WEIGHT	74.85	98.73	75.68	71.69	115.98	94.37	83.71	73.13	148.39
Ovaries (G)	0.248	0.170	0.130	0.186	0.117	0.317	0.151	--	0.055
% BRAIN WEIGHT	11.22	8.30	5.98	9.35	5.92	14.76	7.13	--	2.68
Spleen (G)	0.669	1.026	0.670	0.756	0.789	0.686	0.503	0.663	0.614
% BRAIN WEIGHT	30.26	50.07	30.80	38.01	39.91	31.94	23.75	29.55	29.95

(--)-Data Unavailiable

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

INDIVIDUAL ORGAN WEIGHTS

STUDY: 176
SEX: FEMALE
GROUP: 1-F - VEHICLE (1.67 ml/kg/day)**
ALL FATES DAYS: BEGINNING-29 ALL BALANCES

ANIMAL ID:	320
BALANCE NO.:	
BODY WEIGHT (G)	288
Adrenal Glands (G)	0.093
% BRAIN WEIGHT	4.40
Brain (G)	2.112
Heart (G)	1.054
% BRAIN WEIGHT	49.91
Kidneys (G)	2.605
% BRAIN WEIGHT	123.34
Liver (G)	11.606
% BRAIN WEIGHT	549.53
Lung/Bronchi (G)	1.965
% BRAIN WEIGHT	93.04
Ovaries (G)	0.254
% BRAIN WEIGHT	12.03
Spleen (G)	0.816
% BRAIN WEIGHT	38.64

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD® RATS

INDIVIDUAL ORGAN WEIGHTS

STUDY: 176
SEX: FEMALE
GROUP: 2-F - WR279396 (0.07 ml/kg/day)**
ALL FATES DAYS: BEGINNING-29 ALL BALANCES

ANIMAL ID: / BALANCE NO.:	331	332	333	334	335	336	337	338	339
BODY WEIGHT (G)	269	311	267	318	261	281	292	311	283
Adrenal Glands (G)	0.104	0.095	0.110	0.079	0.085	0.097	0.102	0.106	0.113
% BRAIN WEIGHT	5.30	4.45	5.41	3.81	4.40	4.59	4.76	4.67	5.33
Brain (G)	1.963	2.137	2.035	2.074	1.931	2.112	2.145	2.272	2.120
Heart (G)	0.905	1.088	1.144	1.115	0.785	1.152	1.412	1.077	1.225
% BRAIN WEIGHT	46.10	50.91	56.22	53.76	40.65	54.55	65.83	47.40	57.78
Kidneys (G)	2.792	3.127	2.803	3.546	2.847	2.675	2.265	2.603	2.466
% BRAIN WEIGHT	142.23	146.33	137.74	170.97	147.44	126.66	105.59	114.57	116.32
Liver (G)	11.024	13.014	11.873	14.667	11.259	12.202	11.423	11.120	11.419
% BRAIN WEIGHT	561.59	608.98	583.44	707.18	583.07	577.75	532.54	489.44	538.63
Lung/Bronchi (G)	1.662	1.647	1.911	2.355	1.540	2.050	2.142	1.822	1.998
% BRAIN WEIGHT	84.67	77.07	93.91	113.55	79.75	97.06	99.86	80.19	94.25
Ovaries (G)	0.071	0.227	0.373	0.168	0.139	0.129	0.244	0.207	0.195
% BRAIN WEIGHT	3.62	10.62	18.33	8.10	7.20	6.11	11.38	9.11	9.20
Spleen (G)	0.507	0.720	0.806	0.826	0.561	0.496	0.753	0.864	0.658
% BRAIN WEIGHT	25.83	33.69	39.61	39.83	29.05	23.48	35.10	38.03	31.04

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

INDIVIDUAL ORGAN WEIGHTS

STUDY: 176
SEX: FEMALE

GROUP: 2-F - WR279396 (0.07 ml/kg/day)**
ALL FATES DAYS: BEGINNING-29 ALL BALANCES

ANIMAL ID:	340
BALANCE NO.:	
BODY WEIGHT (G)	287
Adrenal Glands (G)	0.086
% BRAIN WEIGHT	4.26
Brain (G)	2.021
Heart (G)	0.969
% BRAIN WEIGHT	47.95
Kidneys (G)	2.620
% BRAIN WEIGHT	129.64
Liver (G)	12.000
% BRAIN WEIGHT	593.77
Lung/Bronchi (G)	1.449
% BRAIN WEIGHT	71.70
Ovaries (G)	0.187
% BRAIN WEIGHT	9.25
Spleen (G)	0.544
% BRAIN WEIGHT	26.92

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD® RATS

INDIVIDUAL ORGAN WEIGHTS

STUDY: 176
SEX: FEMALE
GROUP: 3-F - WR279396 (0.33 ml/kg/day)**
ALL FATES DAYS: BEGINNING-29 ALL BALANCES

ANIMAL ID: / BALANCE NO.:	351	352	353	354	355	356	357	358	359
BODY WEIGHT (G)	261	286	288	228	249	263	267	323	258
Adrenal Glands (G)	0.117	0.124	0.109	0.103	0.064	0.102	0.088	0.075	0.154
% BRAIN WEIGHT	5.76	5.52	5.41	5.56	3.17	4.86	4.54	3.77	7.20
Brain (G)	2.032	2.248	2.016	1.851	2.019	2.098	1.939	1.988	2.138
Heart (G)	0.834	1.073	1.091	0.700	0.880	0.813	1.009	0.987	1.177
% BRAIN WEIGHT	41.04	47.73	54.12	37.82	43.59	38.75	52.04	49.65	55.05
Kidneys (G)	2.176	2.503	3.082	2.218	2.175	2.599	2.472	3.277	2.963
% BRAIN WEIGHT	107.09	111.34	152.88	119.83	107.73	123.88	127.49	164.84	138.59
Liver (G)	10.480	11.455	12.517	9.606	10.623	10.378	11.237	13.390	10.670
% BRAIN WEIGHT	515.75	509.56	620.88	518.96	526.15	494.66	579.53	673.54	499.06
Lung/Bronchi (G)	1.629	2.415	1.724	1.553	1.821	1.495	1.799	2.147	1.899
% BRAIN WEIGHT	80.17	107.43	85.52	83.90	90.19	71.26	92.78	108.00	88.82
Ovaries (G)	0.223	0.186	0.123	0.133	0.110	0.156	0.143	0.160	0.351
% BRAIN WEIGHT	10.97	8.27	6.10	7.19	5.45	7.44	7.37	8.05	16.42
Spleen (G)	0.650	0.717	0.616	0.591	0.485	0.548	0.684	0.701	0.656
% BRAIN WEIGHT	31.99	31.90	30.56	31.93	24.02	26.12	35.28	35.26	30.68

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INDIVIDUAL ORGAN WEIGHTS

STUDY: 176
SEX: FEMALE

GROUP: 3-F - WR279396 (0.33 ml/kg/day)**
ALL FATES DAYS: BEGINNING-29 ALL BALANCES

ANIMAL ID:	360
BALANCE NO.:	
BODY WEIGHT (G)	310
Adrenal Glands (G)	0.082
% BRAIN WEIGHT	4.69
Brain (G)	1.749
Heart (G)	1.019
% BRAIN WEIGHT	58.26
Kidneys (G)	2.680
% BRAIN WEIGHT	153.23
Liver (G)	13.147
% BRAIN WEIGHT	751.69
Lung/Bronchi (G)	1.949
% BRAIN WEIGHT	111.44
Ovaries (G)	0.108
% BRAIN WEIGHT	6.17
Spleen (G)	0.671
% BRAIN WEIGHT	38.36

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD® RATS

INDIVIDUAL ORGAN WEIGHTS

STUDY: 176
SEX: FEMALE
GROUP: 4-F - WR279396 (1.67 ml/kg/day)**
ALL FATES DAYS: BEGINNING-29 ALL BALANCES

ANIMAL ID: / BALANCE NO.:	371	372	373	374	375	376	377	378	379
BODY WEIGHT (G)	284	286	305	271	305	277	321	268	252
Adrenal Glands (G)	0.081	0.088	0.094	0.089	0.071	0.135	0.120	0.099	0.076
% BRAIN WEIGHT	3.97	4.15	4.50	3.99	3.75	6.61	6.07	4.82	4.04
Brain (G)	2.040	2.123	2.090	2.228	1.894	2.043	1.976	2.052	1.880
Heart (G)	1.068	0.948	1.427	0.808	1.171	0.908	1.039	0.848	0.884
% BRAIN WEIGHT	52.35	44.65	68.28	36.27	61.83	44.44	52.58	41.33	47.02
Kidneys (G)	2.376	2.660	2.910	2.214	2.684	3.050	2.842	2.689	2.661
% BRAIN WEIGHT	116.47	125.29	139.23	99.37	141.71	149.29	143.83	131.04	141.54
Liver (G)	11.284	11.480	14.718	11.460	11.470	11.271	12.806	11.024	9.905
% BRAIN WEIGHT	553.14	540.74	704.21	514.36	605.60	551.69	648.08	537.23	526.86
Lung/Bronchi (G)	1.904	1.710	1.769	1.940	1.964	1.965	1.808	1.801	1.721
% BRAIN WEIGHT	93.33	80.55	84.64	87.07	103.70	96.18	91.50	87.77	91.54
Ovaries (G)	0.170	0.118	0.250	0.114	0.156	0.183	0.134	0.162	0.174
% BRAIN WEIGHT	8.33	5.56	11.96	5.12	8.24	8.96	6.78	7.89	9.26
Spleen (G)	0.701	0.530	0.737	0.579	0.523	0.874	0.554	0.843	0.515
% BRAIN WEIGHT	34.36	24.96	35.26	25.99	27.61	42.78	28.04	41.08	27.39

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD® RATS

INDIVIDUAL ORGAN WEIGHTS

STUDY: 176
SEX: FEMALE
GROUP: 4-F - WR279396 (1.67 ml/kg/day)**
ALL FATES DAYS: BEGINNING-29 ALL BALANCES

ANIMAL ID:	380
BALANCE NO.:	
BODY WEIGHT (G)	255
Adrenal Glands (G)	0.114
% BRAIN WEIGHT	5.39
Brain (G)	2.116
Heart (G)	1.092
% BRAIN WEIGHT	51.61
Kidneys (G)	2.666
% BRAIN WEIGHT	125.99
Liver (G)	10.363
% BRAIN WEIGHT	489.74
Lung/Bronchi (G)	2.205
% BRAIN WEIGHT	104.21
Ovaries (G)	0.170
% BRAIN WEIGHT	8.03
Spleen (G)	0.599
% BRAIN WEIGHT	28.31

**On days 0 - 5, animals received twice the shown volume of test article or vehicle control article daily. On those days, the shown volume was administered at each of two applications, approximately 3 - 4 hours apart.

APPENDIX 9

PATHOLOGY REPORT

AMENDED

FINAL PATHOLOGY REPORT FOR FOUR WEEK TOXICITY STUDY OF WR279396 AFTER DAILY DERMAL APPLICATION IN CD® RATS UIC/TRL STUDY NUMBER 176

PREPARED
BY
PATHOLOGY ASSOCIATES INTERNATIONAL
2201 WEST CAMPBELL PARK DRIVE, SUITE 327
CHICAGO, IL 60612

FOR
TOXICOLOGY RESEARCH LABORATORY (M/C 868)
DEPARTMENT OF PHARMACOLOGY
UNIVERSITY OF ILLINOIS AT CHICAGO
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SEPTEMBER 13, 1995

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study no. 176

Robert S Morrissey 9/28/95
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FINAL REPORT AMENDMENT

STUDY NAME FOUR WEEK DERMAL TOXICITY STUDY OF WR279396 IN CD RATS

STUDY NUMBER UIC/TRL SN 176

DATE OF FINAL REPORT September 13, 1995

PART OF FINAL REPORT TO BE AMENDED (EXACT LOCATION)

1. Title in pages 1, 4, 9, 11-18, 20-27, 29-47, and 49-56.

2. Line 6 and 10 of first paragraph of experimental design and line 1 of third paragraph of experimental design on page 4. Lines 9 and 10 of second paragraph on page 6. Line 6 of third paragraph on page 6. Line 1 of table I on page 7. Line 1 of footnote c and line 1 of footnote ** on page 8.

REASON FOR THE AMENDMENT Sponsor request and protocol amendment.

AMENDMENT (Attach additional sheets as necessary)

1. Change title to "FOUR WEEK TOXICITY STUDY OF WR279396 AFTER DAILY DERMAL APPLICATION IN CD RATS"

2. Change "control", "vehicle", "vehicle control", and/or "vehicle control article" to "placebo (vehicle)" on pages 4, 6, 7 and 8.

APPROVALS --

9/28/95
DATE

R S Morrissey
STUDY PATHOLOGIST

9-28-95
DATE

QUALITY ASSURANCE

TABLE OF CONTENTS

SECTION	TITLE	PAGE
I	Pathology Narrative	3
	Summary of Experimental Design (Table I)	7
	Protocol-Required Tissues (Table II)	7
	Summary of Treatment-Related Lesions (Table III)	8
	Report Codes Table	9
II	Project Summary Table	10
	Males	11
	Females	15
III	Severity Summary Table	19
	Males	20
	Females	24
IV	Tabulated Animal Data	28
	Males	29
	Females	39
V	Correlation of Gross and Microscopic (Micro) Findings	48
	Males	49
	Females	53
VI	Quality Assurance Statement	57

SECTION I

PATHOLOGY NARRATIVE

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FINAL PATHOLOGY REPORT

FOUR WEEK TOXICITY STUDY OF WR279396 AFTER DAILY DERMAL APPLICATION IN CD® RATS

INTRODUCTION

This pathology report, submitted by Pathology Associates International (PAI) to Toxicology Research Laboratory (TRL), University of Illinois at Chicago, represents the histopathology findings for the study designated as "Four Week Toxicity Study of WR279396 After Daily Dermal Application in CD® Rats", UIC/TRL Study Number 176.

EXPERIMENTAL DESIGN AND METHODS

Three groups (Groups 2-4), each composed of 10 male and 10 female CD® (Virus Antibody Free) rats, were initially given the test article twice daily by dermal application for the first five days. The volume of WR279396 administered per application (2 applications/day) was 0.07, 0.33, and 1.67 ml/kg in groups 2, 3, and 4, respectively. This corresponds to a dose of 20, 100, and 500 mg/kg/day of paromomycin + 0.7, 3.3, and 16.7 mg/kg/day of gentamicin, respectively. A placebo (vehicle) group (Group 1) of 10 male and 10 female CD® (Virus Antibody Free) rats received the test article vehicle (Iowa Formulation 232) by dermal application at a dosing volume of 1.67 ml/kg per application. Beginning on Day 6 and for the remainder of the study, due to the appearance of moderate to severe erythema in mid and high dose animals, the volume (amount) of test article or placebo (vehicle) administered was reduced to one-half the initial dose levels. On these days, the volume (amount) was administered once daily in the morning instead of as a split dose twice daily. The total treatment period was 28/29 days starting with Day 0. (See Table I, Summary of Experimental Design).

With the exception of one accidental death (low dose male) on Day 23, all animals were sacrificed and necropsied in random order on Study Days 28 and 29. Animals were anesthetized by Metofane® inhalation (Pitman-Moore, Mundelein, IL) and then perfused transcardially with saline followed by 10% neutral buffered formalin (NBF). All necropsies were performed according to TRL Standard Operating Procedures and were conducted by PAI personnel, except for the low dose male (number 330) which was necropsied on the day of death by an approved TRL technician. Tissues required by the protocol (see Table II, Protocol-Required Tissues) were examined and placed in 10% neutral buffered formalin. Specimens of exposure area skin were collected from the dorsal thoracic region (clipped) and specimens of non-exposure area skin were collected from the dorsal lumbar region (unclipped).

Tissues required for histopathologic evaluation in placebo (vehicle) (Group 1) and high dose (Group 4) groups were trimmed and processed, and slides were prepared in accordance with PAI Standard Operating Procedures. Heads were decalcified and two transverse sections of ear were trimmed to include outer and middle ear in one section and cochlea in the other. These tissues were evaluated by light microscopy and the results were tabulated. Some tissues are inherently difficult to obtain in sections because of their small size (e.g. parathyroid gland and mammary gland). Tissues were recorded as "unsuitable for complete evaluation" when they were missing in both the original section and in recut and retrim attempts to obtain them. Skin, exposure area, was identified as a target organ. Kidneys, ears, sciatic nerve, and exposure area skin were trimmed and

processed, slides were prepared, and the tissues were examined microscopically for animals in the low and mid dose groups. Also, all gross lesions were examined microscopically.

Treatment-related lesions are summarized in Table III, Summary of Treatment-Related Lesions. Microscopic findings for all groups are summarized in the Project Summary Tables (Section II). The mean group severity scores are found in the Severity Summary Tables (Section III). The mean group severity scores were determined by dividing the sum of all severity scores for a finding by the number of tissues examined. Microscopic findings in the protocol-required tissues for individual animals are presented in the Tabulated Animal Data Tables (Section IV). The correlation of the necropsy findings and histopathology findings are reported in the Correlation of Gross and Microscopic (Micro) Findings (Section V). The codes used as entries in these tables are explained in the Report Codes Table.

RESULTS AND DISCUSSION

The Results and Discussion section is divided into three parts: Necropsy Findings, Diagnostic Terms, and Histopathology Findings. The Necropsy Findings portion gives lesions seen at necropsy that were test article-related. The Diagnostic Terms portion lists and clarifies diagnostic terminology that may be unclear. Terms listed in the Diagnostic Terms portion of this section were not necessarily considered to be test article-related. The Histopathology Findings portion of this section reports the results and provides discussion of the histopathologic evaluation of the tissues.

Necropsy Findings

Gross lesions were observed in thymus, mandibular lymph node, eye, adrenal gland, and salivary gland. Gross observations are listed in the Correlation of Gross and Microscopic (Micro) Findings report in Section V. Microscopic findings were correlated with gross lesions when possible. All gross lesions were interpreted as incidental findings.

Diagnostic Terms

The morphologic characteristics of observations and lesions which require comment are presented in subsequent paragraphs to aid in the interpretation of the data.

Skin

Acanthosis was diagnosed when epidermis was focally thickened due to a thicker than normal stratum spinosum layer. Hyperkeratosis was represented by multiple layers of retained keratinized epithelial cells. Scab was diagnosed when a focal accumulation of degenerate inflammatory cells was present in the keratinized layer of epidermis.

Kidney

Mineralization occurred as small foci of deeply basophilic granular material in the lumen of renal tubules at the corticomedullary junction. Chronic inflammation in renal cortex was represented by small foci of mature lymphocytes in interstitium around glomeruli and/or renal tubules. Progressive nephropathy was diagnosed when eosinophilic casts were noted in the lumen of renal tubules and/or when basophilic regenerative epithelium was present.

The remainder of the diagnoses used in this study were considered to be self-explanatory and were not discussed in this section.

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Histopathology Findings:

Skin, exposure site

Local areas of acanthosis were observed in epidermis of skin from exposure area in 0 of 10, 0 of 10, 1 of 10, and 3 of 10 male rats in groups 1, 2, 3, and 4, respectively. In females, similar areas of acanthosis were observed in epidermis of skin from exposure area in 1 of 10, 0 of 10, 0 of 10, and 4 of 10 rats in groups 1, 2, 3, and 4, respectively. Acanthosis was interpreted as a possible response to local irritant effects of the test article.

Hyperkeratosis was observed more frequently in exposure area skin than in non-exposure area skin. In males, hyperkeratosis was present in exposure area skin in 8 of 10, 7 of 10, 8 of 10, and 9 of 10 animals in groups 1, 2, 3, and 4, respectively, while the incidence was 0 of 10 and 2 of 10 in non-exposure area skin for groups 1 and 4, respectively. In females, hyperkeratosis was present in exposure area skin in 8 of 10, 3 of 10, 4 of 10, and 8 of 10 animals in groups 1, 2, 3, and 4, respectively, while the incidence was 1 of 10 and 0 of 10 in non-exposure area skin for groups 1 and 4, respectively. However, the combined administration of paromomycin and gentamicin did not affect the incidence of hyperkeratosis in exposure area skin in either male (8 of 10 vs. 9 of 10 in placebo (vehicle) and high dose males) or female (8 of 10 vs. 8 of 10 in placebo (vehicle) and high dose females) rats. Increased hyperkeratosis in exposure area skin was interpreted as a response to the vehicle and/or a response to rubbing during the application and/or removal of material.

Kidney

The incidence of chronic inflammation in the renal cortex of male rats was 2 of 10, 2 of 10, 3 of 10, and 3 of 10 for groups 1, 2, 3, and 4, respectively. In females, the incidence of chronic inflammation in the renal cortex was 3 of 10, 3 of 10, 2 of 10, and 6 of 10 in groups 1, 2, 3, and 4, respectively. The severity was minimal in all cases, and the change is a relatively common incidental finding. Therefore, I do not consider the slight difference between high dose and placebo (vehicle) females to be biologically significant. Also, the incidence of chronic inflammation in the renal cortex of males was similar in all groups, which further supports the position that the slight increase in incidence in high dose females was not a test article-related effect.

Kidney, exposure area skin, sciatic nerve, and ear were evaluated histopathologically for animal number 330 (low dose male), which was the only early death animal in the study. There was no indication of test article-related toxicity in the tissues evaluated.

CONCLUSIONS

Under the conditions of this study, the daily dermal application of 1.67 ml/kg (1.67 ml/kg x 2 on Days 0-5) of WR279396 to rats for 28/29 days was associated with minimal or mild dermal acanthosis. Daily dermal application of lower volumes of WR279396, 0.33 or 0.07 ml/kg (0.33 or 0.07 ml/kg x 2 on Days 0-5), was not associated with any histologic changes.

Robert L Morrissey
Robert L. Morrissey, DVM, Ph.D.
Diplomate, ACVP

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TABLE I

SUMMARY OF EXPERIMENTAL DESIGN

Treatment Group	Treatment	Paromomycin Dose Level (mg/kg/day)	Gentamicin Dose Level (mg/kg/day)	Dosing Volume (ml/kg/day)	Number of Males	Number of Females
1	Placebo (Vehicle)	0	0	1.67 x 2 (1.67)	10	10
2	WR279396	20 (10)	0.7 (0.04)	0.07 x 2 (0.07)	10	10
3	WR279396	100 (50)	3.3 (1.7)	0.33 x 2 (0.33)	10	10
4	WR279396	500 (250)	16.7 (8.4)	1.67 x 2 (1.67)	10	10

*Numbers in parentheses are dosages for Days 6 through 29.

TABLE II

PROTOCOL-REQUIRED TISSUES

Adrenal glands
Aorta
Brain
Cecum
Colon
Duodenum
Ears (including sensory hair cells of *crista ampullaris*, cochlear and vestibular hair cells, and middle and inner ear)
Epididymides
Esophagus
Eyes
Femur with bone marrow
Heart
Ileum
Jejunum
Kidneys (including proximal tubules of the cortex)
Lacrimal gland (exorbital)
Liver
Lung/Bronchi
Lymph node (mesenteric)
Mammary gland
Ovaries
Pancreas
Pituitary gland
Prostate
Rectum
Salivary gland (submandibular)
Sciatic nerve
Seminal vesicles
Skeletal muscle (thigh)
Skin (exposure and non-exposure areas)
Spinal cord (cervical, mid-thoracic, and lumbar)
Spleen
Sternum with bone marrow
Stomach
Testes
Thymus
Thyroid gland with parathyroids
Trachea
Urinary bladder
Uterus
Vagina
Gross lesions

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AFTER DAILY DERMAL APPLICATION IN CD® RATS
TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 176

Report Codes Table

A. Codes applying to organs

N	Tissues within normal histological limits
A	Autolysis precluding adequate evaluation
O	Paired organ missing
U	Tissues unsuitable for complete evaluation
S	Tissues not applicable to animal
R	Recut
*	Tissues not required by protocol

B. Codes applying to microscopic diagnoses

1	minimal
2	mild
3	moderate
4	marked
( )	focal
[ ]	diffuse
< >	multifocal
P	Present
B	Neoplasm, benign
M	Neoplasm, malignant without metastasis
C	Neoplasm, malignant with metastasis
X	Metastatic site (+)
I	Bilateral
L	Unilateral
-	No data entered

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SECTION II

PROJECT SUMMARY TABLE

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FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD RATS
TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 176

PROJECT SUMMARY

STUDY ID : TRL SN 176 STUDY NUMBER: SN176
FATE: ALL
SEX: MALE

INCIDENCE OF NEOPLASTIC and NON-NEOPLASTIC MICROSCOPIC FINDINGS

GROUP:		1		2		3		4	
NUMBER OF ANIMALS:		10		10		10		10	
		#	%	#	%	#	%	#	%
BRAIN	# EX	10		0		0		10	
Dilatation, ventricle		7	70.0	0	0.0	0	0.0	6	60.0
PITUITARY GLAND	# EX	10		0		0		10	
Cyst, pars distalis		0	0.0	0	0.0	0	0.0	1	10.0
CERVICAL CORD	# EX	10		0		0		10	
Degeneration, neuron		0	0.0	0	0.0	0	0.0	1	10.0
THYMUS	# EX	10		0		0		10	
Hemorrhage, multifocal		8	80.0	0	0.0	0	0.0	7	70.0
SALIVARY GLAND	# EX	10		0		0		10	
Inflammation, chronic		0	0.0	0	0.0	0	0.0	1	10.0
PANCREAS	# EX	10		0		0		10	
Hyperplasia, islet cell		0	0.0	0	0.0	0	0.0	1	10.0
MID-THORACIC CORD	# EX	10		0		0		10	
ADRENAL GLAND	# EX	10		0		0		10	
Ectopic adrenal		2	20.0	0	0.0	0	0.0	0	0.0
Hypertrophy, cortex, multifocal		4	40.0	0	0.0	0	0.0	5	50.0
LUMBAR CORD	# EX	10		0		0		10	
THYROID GLAND	# EX	10		0		0		10	
PARATHYROID GLAND	# EX	9		0		0		8	
TRACHEA	# EX	10		0		0		10	
ESOPHAGUS	# EX	10		0		0		10	

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Incidence Calculated by No. of Tissues Scored

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FOUR WEEK TOXICITY STUDY OF WR279396
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INCIDENCE OF NEOPLASTIC and NON-NEOPLASTIC MICROSCOPIC FINDINGS

GROUP:		1		2		3		4	
NUMBER OF ANIMALS:		10		10		10		10	
		#	%	#	%	#	%	#	%
HEART	# EX	10		0		0		10	
Inflammation, chronic, multifocal		7	70.0	0	0.0	0	0.0	6	60.0
AORTA	# EX	10		0		0		10	
DUODENUM	# EX	10		0		0		10	
COLON	# EX	10		0		0		10	
STOMACH	# EX	10		0		0		10	
LIVER	# EX	10		0		0		10	
Inflammation, chronic, multifocal		8	80.0	0	0.0	0	0.0	8	80.0
Hypertrophy, centrilobular		1	10.0	0	0.0	0	0.0	1	10.0
SPLEEN	# EX	10		0		0		10	
JEJUNUM	# EX	10		0		0		10	
LUNG	# EX	10		0		0		10	
Mineralization, intrinsic artery		3	30.0	0	0.0	0	0.0	2	20.0
Inflammation, acute, peribronchial		1	10.0	0	0.0	0	0.0	0	0.0
Inflammation, acute, perivascular		4	40.0	0	0.0	0	0.0	3	30.0
Inflammation, chronic, interstitium		3	30.0	0	0.0	0	0.0	3	30.0
KIDNEY	# EX	10		10		10		10	
Dilatation, pelvis		1	10.0	1	10.0	2	20.0	0	0.0
Cyst		1	10.0	0	0.0	0	0.0	0	0.0
Inflammation, chronic, cortex		2	20.0	2	20.0	3	30.0	3	30.0
Nephropathy, progressive		1	10.0	0	0.0	1	10.0	3	30.0
Mineralization		0	0.0	1	10.0	0	0.0	0	0.0
URINARY BLADDER	# EX	10		0		0		10	

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INCIDENCE OF NEOPLASTIC and NON-NEOPLASTIC MICROSCOPIC FINDINGS

GROUP:		1		2		3		4	
NUMBER OF ANIMALS:		10		10		10		10	
		#	%	#	%	#	%	#	%
PROSTATE	# EX	10		0		0		10	
Inflammation, chronic		0	0.0	0	0.0	0	0.0	1	10.0
SKIN (EXPOSURE AREA)	# EX	10		10		10		10	
Hyperkeratosis		8	80.0	7	70.0	8	80.0	9	90.0
Acanthosis		0	0.0	0	0.0	1	10.0	3	30.0
Inflammation, chronic, subepidermal		0	0.0	0	0.0	2	20.0	0	0.0
Scab		0	0.0	0	0.0	1	10.0	0	0.0
SKIN (NON-EXPOSURE AREA)	# EX	10		0		0		10	
Hyperkeratosis		0	0.0	0	0.0	0	0.0	2	20.0
MAMMARY GLAND	# EX	10		0		0		9	
ILEUM	# EX	10		0		0		10	
CECUM	# EX	10		0		0		10	
LYMPH NODE, MESENTERIC	# EX	10		0		0		10	
Hemorrhage		1	10.0	0	0.0	0	0.0	0	0.0
SKELETAL MUSCLE	# EX	10		0		0		10	
SCIATIC NERVE	# EX	10		10		10		10	
RECTUM	# EX	10		0		0		10	
TESTES	# EX	10		0		0		10	
EPIDIDYMIS	# EX	10		0		0		10	
Inflammation, chronic		0	0.0	0	0.0	0	0.0	1	10.0
SEMINAL VESICLE	# EX	10		0		0		10	

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PROJECT SUMMARY

STUDY ID : TRL SN 176 STUDY NUMBER: SN176
FATE: ALL
SEX: MALE

INCIDENCE OF NEOPLASTIC and NON-NEOPLASTIC MICROSCOPIC FINDINGS

GROUP:		1		2		3		4	
NUMBER OF ANIMALS:		10		10		10		10	
		#	%	#	%	#	%	#	%
EAR	# EX	10		10		10		10	
FEMUR	# EX	10		0		0		10	
STERNUM	# EX	10		0		0		10	
BONE MARROW	# EX	10		0		0		10	
EYE	# EX	10		1		0		10	
Inflammation, subacute, periorbital		1	10.0	0	0.0	0	0.0	2	20.0
Hemorrhage, periorbital		0	0.0	1	100.0	0	0.0	0	0.0
LACRIMAL GLAND	# EX	10		0		0		10	
Inflammation, chronic		2	20.0	0	0.0	0	0.0	2	20.0
LYMPH NODE, MANDIBULAR	# EX	1		1		1		2	
Hemorrhage		1	100.0	0	0.0	1	100.0	1	50.0
Hyperplasia, lymphoid		0	0.0	1	100.0	1	100.0	1	50.0

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PROJECT SUMMARY

STUDY ID : TRL SN 176 STUDY NUMBER: SN176
FATE: ALL
SEX: FEMALE

INCIDENCE OF NEOPLASTIC and NON-NEOPLASTIC MICROSCOPIC FINDINGS

GROUP:		1		2		3		4	
NUMBER OF ANIMALS:		10		10		10		10	
		#	%	#	%	#	%	#	%
BRAIN	# EX	10		0		0		10	
Dilatation, ventricle		2	20.0	0	0.0	0	0.0	3	30.0
PITUITARY GLAND	# EX	10		0		0		10	
CERVICAL CORD	# EX	10		0		0		10	
THYMUS	# EX	10		0		0		10	
Hemorrhage, multifocal		1	10.0	0	0.0	0	0.0	3	30.0
SALIVARY GLAND	# EX	10		0		1		10	
Inflammation, chronic		0	0.0	0	0.0	0	0.0	1	10.0
PANCREAS	# EX	10		0		0		10	
Hyperplasia, islet cell		1	10.0	0	0.0	0	0.0	0	0.0
Atrophy, acinar		0	0.0	0	0.0	0	0.0	1	10.0
MID-THORACIC CORD	# EX	10		0		0		10	
Chromatolysis, neuron		1	10.0	0	0.0	0	0.0	0	0.0
ADRENAL GLAND	# EX	10		0		0		10	
Ectopic adrenal		2	20.0	0	0.0	0	0.0	0	0.0
Hypertrophy, cortex, multifocal		5	50.0	0	0.0	0	0.0	4	40.0
LUMBAR CORD	# EX	10		0		0		10	
THYROID GLAND	# EX	10		0		0		10	
PARATHYROID GLAND	# EX	8		0		0		8	
TRACHEA	# EX	10		0		0		10	
ESOPHAGUS	# EX	10		0		0		10	

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GROUP:		1		2		3		4	
NUMBER OF ANIMALS:		10		10		10		10	
		#	%	#	%	#	%	#	%
HEART	# EX	10		0		0		10	
Inflammation, chronic, multifocal		7	70.0	0	0.0	0	0.0	5	50.0
AORTA	# EX	10		0		0		10	
DUODENUM	# EX	10		0		0		10	
COLON	# EX	10		0		0		10	
STOMACH	# EX	10		0		0		10	
LIVER	# EX	10		0		0		10	
Inflammation, chronic, multifocal		8	80.0	0	0.0	0	0.0	8	80.0
SPLEEN	# EX	10		0		0		10	
JEJUNUM	# EX	10		0		0		10	
LUNG	# EX	10		0		0		10	
Mineralization, intrinsic artery		2	20.0	0	0.0	0	0.0	2	20.0
Inflammation, acute, perivascular		7	70.0	0	0.0	0	0.0	6	60.0
Inflammation, chronic, interstitium		1	10.0	0	0.0	0	0.0	1	10.0
Inflammation, pyogranulomatous, focal		5	50.0	0	0.0	0	0.0	6	60.0
Hemorrhage		2	20.0	0	0.0	0	0.0	4	40.0
KIDNEY	# EX	10		10		10		10	
Dilatation, pelvis		0	0.0	0	0.0	1	10.0	0	0.0
Cyst		0	0.0	1	10.0	0	0.0	0	0.0
Inflammation, chronic, cortex		3	30.0	3	30.0	2	20.0	6	60.0
Nephropathy, progressive		3	30.0	1	10.0	2	20.0	3	30.0
Mineralization		9	90.0	6	60.0	6	60.0	7	70.0
URINARY BLADDER	# EX	10		0		0		10	

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PATHOLOGY ASSOCIATES INTERNATIONAL
FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD RATS
TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 176

PROJECT SUMMARY

STUDY IO : TRL SN 176 STUDY NUMBER: SN176
FATE: ALL
SEX: FEMALE

INCIDENCE OF NEOPLASTIC and NON-NEOPLASTIC MICROSCOPIC FINDINGS

GROUP:		1		2		3		4	
NUMBER OF ANIMALS:		10		10		10		10	
		#	%	#	%	#	%	#	%
SKIN (EXPOSURE AREA)	# EX	10		10		10		10	
Hyperkeratosis		8	80.0	3	30.0	4	40.0	8	80.0
Acanthosis		1	10.0	0	0.0	0	0.0	4	40.0
SKIN (NON-EXPOSURE AREA)	# EX	10		0		0		10	
Hyperkeratosis		1	10.0	0	0.0	0	0.0	0	0.0
MAMMARY GLAND	# EX	10		0		0		10	
ILEUM	# EX	10		0		0		10	
CECUM	# EX	10		0		0		10	
LYMPH NODE, MESENTERIC	# EX	10		0		0		10	
SKELETAL MUSCLE	# EX	10		0		0		10	
SCIATIC NERVE	# EX	10		10		10		10	
RECTUM	# EX	10		0		0		10	
OVARY	# EX	10		0		0		10	
UTERUS	# EX	10		0		0		10	
Dilatation		5	50.0	0	0.0	0	0.0	1	10.0
VAGINA	# EX	10		0		0		10	
EAR	# EX	10		10		10		10	
FEMUR	# EX	10		0		0		10	
STERNUM	# EX	10		0		0		10	

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PATHOLOGY ASSOCIATES INTERNATIONAL
FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD RATS
TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 176

PROJECT SUMMARY

STUDY ID : TRL SN 176 STUDY NUMBER: SN176
FATE: ALL
SEX: FEMALE

INCIDENCE OF NEOPLASTIC and NON-NEOPLASTIC MICROSCOPIC FINDINGS

GROUP:		1		2		3		4	
NUMBER OF ANIMALS:		10		10		10		10	
		#	%	#	%	#	%	#	%
BONE MARROW	# EX	10		0		0		10	
EYE	# EX	10		0		0		10	
Inflammation, subacute, periorbital		3	30.0	0	0.0	0	0.0	5	50.0
LACRIMAL GLAND	# EX	10		0		0		10	
Inflammation, chronic		2	20.0	0	0.0	0	0.0	3	30.0
LYMPH NODE, MANDIBULAR	# EX	2		1		1		0	
Hyperplasia, lymphoid		1	50.0	1	100.0	1	100.0	0	0.0
Accumulation, plasma cell		1	50.0	0	0.0	1	100.0	0	0.0

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study no. 176
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SECTION III

SEVERITY SUMMARY TABLE

PATHOLOGY ASSOCIATES INTERNATIONAL
FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD RATS
TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 176

SEVERITY SUMMARY

STUDY ID : TRL SN 176 STUDY NUMBER: SN176
FATE: ALL
SEX: MALE

GROUP:		1	2	3	4
NUMBER OF ANIMALS:		10	10	10	10
		# SEV	# SEV	# SEV	# SEV
BRAIN	# EX	10	0	0	10
Dilatation, ventricle		7 1.00	0 0.00	0 0.00	6 0.70
PITUITARY GLAND	# EX	10	0	0	10
Cyst, pars distalis		0 0.00	0 0.00	0 0.00	1 0.20
CERVICAL CORD	# EX	10	0	0	10
Degeneration, neuron		0 0.00	0 0.00	0 0.00	1 0.10
THYMUS	# EX	10	0	0	10
Hemorrhage, multifocal		8 1.10	0 0.00	0 0.00	7 0.70
SALIVARY GLAND	# EX	10	0	0	10
Inflammation, chronic		0 0.00	0 0.00	0 0.00	1 0.10
PANCREAS	# EX	10	0	0	10
Hyperplasia, islet cell		0 0.00	0 0.00	0 0.00	1 0.10
MID-THORACIC CORD	# EX	10	0	0	10
ADRENAL GLAND	# EX	10	0	0	10
Ectopic adrenal		2 0.20	0 0.00	0 0.00	0 0.00
Hypertrophy, cortex, multifocal		4 0.40	0 0.00	0 0.00	5 0.50
LUMBAR CORD	# EX	10	0	0	10
THYROID GLAND	# EX	10	0	0	10
PARATHYROID GLAND	# EX	9	0	0	8
TRACHEA	# EX	10	0	0	10
ESOPHAGUS	# EX	10	0	0	10

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25-SEP-1995

PATHOLOGY ASSOCIATES INTERNATIONAL
FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD RATS
TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 176

SEVERITY SUMMARY

STUDY ID : TRL SN 176 STUDY NUMBER: SN176
FATE: ALL
SEX: MALE

GROUP:		1	2	3	4
NUMBER OF ANIMALS:		10	10	10	10
		# SEV	# SEV	# SEV	# SEV
HEART	# EX	10	0	0	10
Inflammation, chronic, multifocal		7 0.90	0 0.00	0 0.00	6 0.80
AORTA	# EX	10	0	0	10
DUODENUM	# EX	10	0	0	10
COLON	# EX	10	0	0	10
STOMACH	# EX	10	0	0	10
LIVER	# EX	10	0	0	10
Inflammation, chronic, multifocal		8 0.80	0 0.00	0 0.00	8 0.80
Hypertrophy, centrilobular		1 0.10	0 0.00	0 0.00	1 0.10
SPLEEN	# EX	10	0	0	10
JEJUNUM	# EX	10	0	0	10
LUNG	# EX	10	0	0	10
Mineralization, intrinsic artery		3 0.30	0 0.00	0 0.00	2 0.20
Inflammation, acute, peribronchial		1 0.20	0 0.00	0 0.00	0 0.00
Inflammation, acute, perivascular		4 0.40	0 0.00	0 0.00	3 0.60
Inflammation, chronic, interstitium		3 0.30	0 0.00	0 0.00	3 0.30
KIDNEY	# EX	10	10	10	10
Dilatation, pelvis		1 0.10	1 0.20	2 0.30	0 0.00
Cyst		1 0.20	0 0.00	0 0.00	0 0.00
Inflammation, chronic, cortex		2 0.20	2 0.20	3 0.30	3 0.30
Nephropathy, progressive		1 0.10	0 0.00	1 0.10	3 0.30
Mineralization		0 0.00	1 0.10	0 0.00	0 0.00
URINARY BLADDER	# EX	10	0	0	10

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25-SEP-1995

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FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD RATS
TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 176

SEVERITY SUMMARY

STUDY ID : TRL SN 176 STUDY NUMBER: SN176
FATE: ALL
SEX: MALE

GROUP:		1	2	3	4
NUMBER OF ANIMALS:		10	10	10	10
		# SEV	# SEV	# SEV	# SEV
PROSTATE	# EX	10	0	0	10
Inflammation, chronic		0 0.00	0 0.00	0 0.00	1 0.10
SKIN (EXPOSURE AREA)	# EX	10	10	10	10
Hyperkeratosis		8 1.00	7 0.70	8 0.80	9 1.20
Acanthosis		0 0.00	0 0.00	1 0.10	3 0.30
Inflammation, chronic, subepidermal		0 0.00	0 0.00	2 0.20	0 0.00
Scab		0 0.00	0 0.00	1 0.10	0 0.00
SKIN (NON-EXPOSURE AREA)	# EX	10	0	0	10
Hyperkeratosis		0 0.00	0 0.00	0 0.00	2 0.20
MAMMARY GLAND	# EX	10	0	0	9
ILEUM	# EX	10	0	0	10
CECUM	# EX	10	0	0	10
LYMPH NODE, MESENTERIC	# EX	10	0	0	10
Hemorrhage		1 0.10	0 0.00	0 0.00	0 0.00
SKELETAL MUSCLE	# EX	10	0	0	10
SCIATIC NERVE	# EX	10	10	10	10
RECTUM	# EX	10	0	0	10
TESTES	# EX	10	0	0	10
EPIDIDYMIS	# EX	10	0	0	10
Inflammation, chronic		0 0.00	0 0.00	0 0.00	1 0.10
SEMINAL VESICLE	# EX	10	0	0	10

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FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD RATS
TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 176

SEVERITY SUMMARY

STUDY ID : TRL SN 176 STUDY NUMBER: SN176
FATE: ALL
SEX: MALE

GROUP:		1		2		3		4	
NUMBER OF ANIMALS:		10		10		10		10	
		#	SEV	#	SEV	#	SEV	#	SEV
EAR	# EX	10		10		10		10	
FEMUR	# EX	10		0		0		10	
STERNUM	# EX	10		0		0		10	
BONE MARROW	# EX	10		0		0		10	
EYE	# EX	10		1		0		10	
Inflammation, subacute, periorbital		1	0.20	0	0.00	0	0.00	2	0.20
Hemorrhage, periorbital		0	0.00	1	2.00	0	0.00	0	0.00
LACRIMAL GLAND	# EX	10		0		0		10	
Inflammation, chronic		2	0.20	0	0.00	0	0.00	2	0.20
LYMPH NODE, MANDIBULAR	# EX	1		1		1		2	
Hemorrhage		1	1.00	0	0.00	1	2.00	1	0.50
Hyperplasia, lymphoid		0	0.00	1	3.00	1	1.00	1	1.00

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FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD RATS
TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 176

SEVERITY SUMMARY

STUDY ID : TRL SN 176 STUDY NUMBER: SN176
FATE: ALL
SEX: FEMALE

GROUP:		1	2	3	4
NUMBER OF ANIMALS:		10	10	10	10
		# SEV	# SEV	# SEV	# SEV
BRAIN	# EX	10	0	0	10
Dilatation, ventricle		2 0.20	0 0.00	0 0.00	3 0.30
PITUITARY GLAND	# EX	10	0	0	10
CERVICAL CORD	# EX	10	0	0	10
THYMUS	# EX	10	0	0	10
Hemorrhage, multifocal		1 0.10	0 0.00	0 0.00	3 0.30
SALIVARY GLAND	# EX	10	0	1	10
Inflammation, chronic		0 0.00	0 0.00	0 0.00	1 0.10
PANCREAS	# EX	10	0	0	10
Hyperplasia, islet cell		1 0.10	0 0.00	0 0.00	0 0.00
Atrophy, acinar		0 0.00	0 0.00	0 0.00	1 0.10
MID-THORACIC CORD	# EX	10	0	0	10
Chromatolysis, neuron		1 0.10	0 0.00	0 0.00	0 0.00
ADRENAL GLAND	# EX	10	0	0	10
Ectopic adrenal		2 0.20	0 0.00	0 0.00	0 0.00
Hypertrophy, cortex, multifocal		5 0.50	0 0.00	0 0.00	4 0.40
LUMBAR CORD	# EX	10	0	0	10
THYROID GLAND	# EX	10	0	0	10
PARATHYROID GLAND	# EX	8	0	0	8
TRACHEA	# EX	10	0	0	10
ESOPHAGUS	# EX	10	0	0	10

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study no. 176

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FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD RATS
TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 176

SEVERITY SUMMARY

STUDY ID : TRL SN 176 STUDY NUMBER: SN176
FATE: ALL
SEX: FEMALE

GROUP:		1	2	3	4
NUMBER OF ANIMALS:		10	10	10	10
		# SEV	# SEV	# SEV	# SEV
HEART	# EX	10	0	0	10
Inflammation, chronic, multifocal		7 0.70	0 0.00	0 0.00	5 0.60
AORTA	# EX	10	0	0	10
DUODENUM	# EX	10	0	0	10
COLON	# EX	10	0	0	10
STOMACH	# EX	10	0	0	10
LIVER	# EX	10	0	0	10
Inflammation, chronic, multifocal		8 0.80	0 0.00	0 0.00	8 0.80
SPLEEN	# EX	10	0	0	10
JEJUNUM	# EX	10	0	0	10
LUNG	# EX	10	0	0	10
Mineralization, intrinsic artery		2 0.20	0 0.00	0 0.00	2 0.20
Inflammation, acute, perivascular		7 0.90	0 0.00	0 0.00	6 0.60
Inflammation, chronic, interstitium		1 0.10	0 0.00	0 0.00	1 0.10
Inflammation, pyogranulomatous, focal		5 0.50	0 0.00	0 0.00	6 0.60
Hemorrhage		2 0.20	0 0.00	0 0.00	4 0.40
KIDNEY	# EX	10	10	10	10
Dilatation, pelvis		0 0.00	0 0.00	1 0.10	0 0.00
Cyst		0 0.00	1 0.10	0 0.00	0 0.00
Inflammation, chronic, cortex		3 0.30	3 0.30	2 0.20	6 0.60
Nephropathy, progressive		3 0.30	1 0.10	2 0.20	3 0.30
Mineralization		9 1.20	6 0.70	6 0.60	7 0.80
URINARY BLADDER	# EX	10	0	0	10

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FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD RATS
TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 176

SEVERITY SUMMARY

STUDY ID : TRL SN 176 STUDY NUMBER: SN176
FATE: ALL
SEX: FEMALE

GROUP:		1	2	3	4
NUMBER OF ANIMALS:		10	10	10	10
		# SEV	# SEV	# SEV	# SEV
SKIN (EXPOSURE AREA)	# EX	10	10	10	10
Hyperkeratosis		8 0.80	3 0.30	4 0.40	8 0.80
Acanthosis		1 0.10	0 0.00	0 0.00	4 0.50
SKIN (NON-EXPOSURE AREA)	# EX	10	0	0	10
Hyperkeratosis		1 0.10	0 0.00	0 0.00	0 0.00
MAMMARY GLAND	# EX	10	0	0	10
ILEUM	# EX	10	0	0	10
CECUM	# EX	10	0	0	10
LYMPH NODE, MESENTERIC	# EX	10	0	0	10
SKELETAL MUSCLE	# EX	10	0	0	10
SCIATIC NERVE	# EX	10	10	10	10
RECTUM	# EX	10	0	0	10
OVARY	# EX	10	0	0	10
UTERUS	# EX	10	0	0	10
Dilatation		5 1.00	0 0.00	0 0.00	1 0.20
VAGINA	# EX	10	0	0	10
EAR	# EX	10	10	10	10
FEMUR	# EX	10	0	0	10
STERNUM	# EX	10	0	0	10

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study no. 176

R S Morrissey 9/28/95
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25-SEP-1995

PATHOLOGY ASSOCIATES INTERNATIONAL
FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD RATS
TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 176

SEVERITY SUMMARY

STUDY ID : TRL SN 176 STUDY NUMBER: SN176
FATE: ALL
SEX: FEMALE

GROUP:		1	2	3	4
NUMBER OF ANIMALS:		10	10	10	10
		# SEV	# SEV	# SEV	# SEV
BONE MARROW	# EX	10	0	0	10
EYE	# EX	10	0	0	10
Inflammation, subacute, periorbital		3 0.30	0 0.00	0 0.00	5 0.70
LACRIMAL GLAND	# EX	10	0	0	10
Inflammation, chronic		2 0.20	0 0.00	0 0.00	3 0.30
LYMPH NODE, MANDIBULAR	# EX	2	1	1	0
Hyperplasia, lymphoid		1 1.00	1 2.00	1 3.00	0 0.00
Accumulation, plasma cell		1 1.00	0 0.00	1 2.00	0 0.00

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study no. 176
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SECTION IV

TABULATED ANIMAL DATA

PATHOLOGY ASSOCIATES INTERNATIONAL
FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD RATS
TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 176

TABULATED ANIMAL DATA

STUDY ID : TRL SN 176
FATE: ALL

STUDY NUMBER: SN176
GROUP: 1
SEX: MALE

ANIMAL ID:	301	302	303	304	305	306	307	308	309	310
BRAIN	N		N	N						
Dilatation, ventricle	-	3	-	-	1	1	1	1	2	1
PITUITARY GLAND	N	N	N	N	N	N	N	N	N	N
CERVICAL CORD	N	N	N	N	N	N	N	N	N	N
THYMUS							N			N
Hemorrhage, multifocal	2	1	1	1	1	2	-	2	1	-
SALIVARY GLAND	N	N	N	N	N	N	N	N	N	N
PANCREAS	N	N	N	N	N	N	N	N	N	N
MID-THORACIC CORD	N	N	N	N	N	N	N	N	N	N
ADRENAL GLAND	N		N	N				N		N
Ectopic adrenal	-	1	-	-	-	-	-	-	1	-
Hypertrophy, cortex, multifocal	-	1	-	-	1	1	1	-	-	-
LUMBAR CORD	N	N	N	N	N	N	N	N	N	N
THYROID GLAND	N	N	N	N	N	N	N	N	N	N
PARATHYROID GLAND	N	N	N	N	U	N	N	N	N	N
TRACHEA	N	N	N	N	N	N	N	N	N	N
ESOPHAGUS	N	N	N	N	N	N	N	N	N	N
HEART		N		N					N	
Inflammation, chronic, multifocal	1	-	1	-	1	1	3	1	-	1

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See Reports Code Table for Symbol Definitions

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FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD RATS
TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 176

TABULATED ANIMAL DATA

STUDY ID : TRL SN 176
FATE: ALL

STUDY NUMBER: SN176
GROUP: 1
SEX: MALE

ANIMAL ID:	301	302	303	304	305	306	307	308	309	310
AORTA	N	N	N	N	N	N	N	N	N	N
DUODENUM	N	N	N	N	N	N	N	N	N	N
COLON	N	N	N	N	N	N	N	N	N	N
STOMACH	N	N	N	N	N	N	N	N	N	N
LIVER							N	N		
Inflammation, chronic, multifocal	1	1	1	1	1	1	-	-	1	1
Hypertrophy, centrilobular	-	-	-	1	-	-	-	-	-	-
SPLEEN	N	N	N	N	N	N	N	N	N	N
JEJUNUM	N	N	N	N	N	N	N	N	N	N
LUNG	N			N					N	
Mineralization, intrinsic artery	-	1	-	-	1	-	-	1	-	-
Inflammation, acute, peribronchial	-	-	2	-	-	-	-	-	-	-
Inflammation, acute, perivascular	-	-	1	-	1	1	1	-	-	-
Inflammation, chronic, interstitium	-	-	-	-	-	1	1	-	-	1
KIDNEY	N	N	N	N	N	N				N
Dilatation, pelvis	-	-	-	-	-	-	1	-	-	-
Cyst	-	-	-	-	-	-	-	2	-	-
Inflammation, chronic, cortex	-	-	-	-	-	-	-	1	1	-
Nephropathy, progressive	-	-	-	-	-	-	-	1	-	-
URINARY BLADDER	N	N	N	N	N	N	N	N	N	N
PROSTATE	N	N	N	N	N	N	N	N	N	N
SKIN (EXPOSURE AREA)	N								N	
Hyperkeratosis	-	1	2	2	1	1	1	1	-	1

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study no. 176

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FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD RATS
TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 176

TABULATED ANIMAL DATA

STUDY ID : TRL SN 176
FATE: ALL

STUDY NUMBER: SN176
GROUP: 1
SEX: MALE

ANIMAL ID:	301	302	303	304	305	306	307	308	309	310
SKIN (NON-EXPOSURE AREA)	N	N	N	N	N	N	N	N	N	N
MAMMARY GLAND	N	N	N	N	N	N	N	N	N	N
ILEUM	N	N	N	N	N	N	N	N	N	N
CECUM	N	N	N	N	N	N	N	N	N	N
LYMPH NODE, MESENTERIC	N	N	N	N	N	N	N	N		N
Hemorrhage	-	-	-	-	-	-	-	-	1	-
SKELETAL MUSCLE	N	N	N	N	N	N	N	N	N	N
SCIATIC NERVE	N	N	N	N	N	N	N	N	N	N
RECTUM	N	N	N	N	N	N	N	N	N	N
TESTES	N	N	N	N	N	N	N	N	N	N
EPIDIDYMIS	N	N	N	N	N	N	N	N	N	N
SEMINAL VESICLE	N	N	N	N	N	N	N	N	N	N
EAR	N	N	N	N	N	N	N	N	N	N
FEMUR	N	N	N	N	N	N	N	N	N	N
STERNUM	N	N	N	N	N	N	N	N	N	N
BONE MARROW	N	N	N	N	N	N	N	N	N	N
EYE	N	N	N	N	N	N		N	N	N
Inflammation, subacute, periorbital	-	-	-	-	-	-	2	-	-	-
LACRIMAL GLAND	N	N		N	N	N	N	N	N	

THIS PAGE REVISED

See Reports Code Table for Symbol Definitions

study no. 176

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signature date

25-SEP-1995

PATHOLOGY ASSOCIATES INTERNATIONAL
FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD RATS
TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 176

TABULATED ANIMAL DATA

STUDY ID : TRL SN 176 STUDY NUMBER: SN176
FATE: ALL GROUP: 1
SEX: MALE

ANIMAL ID:	301	302	303	304	305	306	307	308	309	310
LACRIMAL GLAND	N	N		N	N	N	N	N	N	
Inflammation, chronic	-	-	1	-	-	-	-	-	-	1
LYMPH NODE, MANDIBULAR										
Hemorrhage	-	-	-	-	-	-	1	-	-	-

THIS PAGE REVISED

See Reports Code Table for Symbol Definitions

study no. 176

RS Morrissey 9/28/95
signature date

25-SEP-1995

PATHOLOGY ASSOCIATES INTERNATIONAL
FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD RATS
TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 176

TABULATED ANIMAL DATA

STUDY ID : TRL SN 176 STUDY NUMBER: SN176
FATE: ALL GROUP: 2
SEX: MALE

ANIMAL ID:	321	322	323	324	325	326	327	328	329	330
KIDNEY					N	N	N	N	N	N
Dilatation, pelvis	2	-	-	-	-	-	-	-	-	-
Inflammation, chronic, cortex	-	1	-	1	-	-	-	-	-	-
Mineralization	-	-	1	-	-	-	-	-	-	-
SKIN (EXPOSURE AREA)						N	N	N		
Hyperkeratosis	1	1	1	1	1	-	-	-	1	1
SCIATIC NERVE	N	N	N	N	N	N	N	N	N	N
EAR	N	N	N	N	N	N	N	N	N	N
EYE										
Hemorrhage, periorbital	-	-	-	-	-	2	-	-	-	-
LYMPH NODE, MANDIBULAR										
Hyperplasia, lymphoid	3	-	-	-	-	-	-	-	-	-

THIS PAGE REVISED

See Reports Code Table for Symbol Definitions

study no. 176

RB Morrissey 9/28/95
signature date

25-SEP-1995

PATHOLOGY ASSOCIATES INTERNATIONAL
FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD RATS
TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 176

TABULATED ANIMAL DATA

STUDY ID : TRL SN 176 — STUDY NUMBER: SN176
FATE: ALL — GROUP: 3
SEX: MALE

ANIMAL ID:	341	342	343	344	345	346	347	348	349	350
KIDNEY	N	N				N	N	N	N	
Dilatation, pelvis	-	-	1	-	-	-	-	-	-	2
Inflammation, chronic, cortex	-	-	1	1	-	-	-	-	-	1
Nephropathy, progressive	-	-	-	-	1	-	-	-	-	-
SKIN (EXPOSURE AREA)					N					
Hyperkeratosis	1	1	1	1	-	1	-	1	1	1
Acanthosis	-	-	1	-	-	-	-	-	-	-
Inflammation, chronic, subepidermal	-	-	1	-	-	-	1	-	-	-
Scab	-	-	-	-	-	-	1	-	-	-
SCIATIC NERVE	N	N	N	N	N	N	N	N	N	N
EAR	N	N	N	N	N	N	N	N	N	N
LYMPH NODE, MANDIBULAR										
Hemorrhage	2	-	-	-	-	-	-	-	-	-
Hyperplasia, lymphoid	1	-	-	-	-	-	-	-	-	-

THIS PAGE REVISED

study no. 176

RS Morrissey 9/28/95
signature date

See Reports Code Table for Symbol Definitions

25-SEP-1995

PATHOLOGY ASSOCIATES INTERNATIONAL
FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD RATS
TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 176

TABULATED ANIMAL DATA

STUDY ID : TRL SN 176
FATE: ALL

STUDY NUMBER: SN176
GROUP: 4
SEX: MALE

ANIMAL ID:	361	362	363	364	365	366	367	368	369	370
BRAIN	N			N	N			N		
Dilatation, ventricle	-	1	2	-	-	1	1	-	1	1
PITUITARY GLAND	N	N	N	N		N	N	N	N	N
Cyst, pars distalis	-	-	-	-	2	-	-	-	-	-
CERVICAL CORD	N	N	N	N		N	N	N	N	N
Degeneration, neuron	-	-	-	-	1	-	-	-	-	-
THYMUS				N	N					N
Hemorrhage, multifocal	1	1	1	-	-	1	1	1	1	-
SALIVARY GLAND		N	N	N	N	N	N	N	N	N
Inflammation, chronic	1	-	-	-	-	-	-	-	-	-
PANCREAS	N	N	N	N	N	N		N	N	N
Hyperplasia, islet cell	-	-	-	-	-	-	1	-	-	-
MID-THORACIC CORD	N	N	N	N	N	N	N	N	N	N
ADRENAL GLAND	N		N	N					N	N
Hypertrophy, cortex, multifocal	-	1	-	-	1	1	1	1	-	-
LUMBAR CORD	N	N	N	N	N	N	N	N	N	N
THYROID GLAND	N	N	N	N	N	N	N	N	N	N
PARATHYROID GLAND	N	N	N	U	N	N	U	N	N	N
TRACHEA	N	N	N	N	N	N	N	N	N	N
ESOPHAGUS	N	N	N	N	N	N	N	N	N	N
HEART	N				N		N		N	
Inflammation, chronic, multifocal	-	3	1	1	-	1	-	1	-	1

THIS PAGE REVISED

study no. 176

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See Reports Code Table for Symbol Definitions

25-SEP-1995

PATHOLOGY ASSOCIATES INTERNATIONAL
FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD RATS
TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 176

TABULATED ANIMAL DATA

STUDY ID : TRL SN 176 — STUDY NUMBER: SN176
FATE: ALL — GROUP: 4
SEX: MALE

ANIMAL ID:	361	362	363	364	365	366	367	368	369	370
AORTA	N	N	N	N	N	N	N	N	N	N
DUODENUM	N	N	N	N	N	N	N	N	N	N
COLON	N	N	N	N	N	N	N	N	N	N
STOMACH	N	N	N	N	N	N	N	N	N	N
LIVER		N			N					
Inflammation, chronic, multifocal	1	-	1	1	-	1	1	1	1	1
Hypertrophy, centrilobular	-	-	-	-	-	-	-	1	-	-
SPLEEN	N	N	N	N	N	N	N	N	N	N
JEJUNUM	N	N	N	N	N	N	N	N	N	N
LUNG					N	N				N
Mineralization, intrinsic artery	1	-	-	-	-	-	1	-	-	-
Inflammation, acute, perivascular	-	2	2	2	-	-	-	-	-	-
Inflammation, chronic, interstitium	-	-	1	-	-	-	-	1	1	-
KIDNEY		N	N		N		N	N		N
Inflammation, chronic, cortex	1	-	-	1	-	-	-	-	1	-
Nephropathy, progressive	1	-	-	-	-	1	-	-	1	-
URINARY BLADDER	N	N	N	N	N	N	N	N	N	N
PROSTATE	N	N	N	N	N	N	N	N	N	
Inflammation, chronic	-	-	-	-	-	-	-	-	-	1
SKIN (EXPOSURE AREA)			N							
Hyperkeratosis	1	1	-	1	1	2	2	1	2	1
Acanthosis	-	-	-	1	-	-	1	-	1	-
SKIN (NON-EXPOSURE AREA)	N	N	N	N	N			N	N	N

THIS PAGE REVISED

study no. 176

R E Morrissey 9/28/95
signature date

See Reports Code Table for Symbol Definitions

25-SEP-1995

PATHOLOGY ASSOCIATES INTERNATIONAL
FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD RATS
TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 176

TABULATED ANIMAL DATA

STUDY ID : TRL SN 176
FATE: ALL

STUDY NUMBER: SN176
GROUP: 4
SEX: MALE

ANIMAL ID:	361	362	363	364	365	366	367	368	369	370
SKIN (NON-EXPOSURE AREA)	N	N	N	N	N			N	N	N
Hyperkeratosis	-	-	-	-	-	1	1	-	-	-
MAMMARY GLAND	N	N	N	N	N	N	N	N	U	N
ILEUM	N	N	N	N	N	N	N	N	N	N
CECUM	N	N	N	N	N	N	N	N	N	N
LYMPH NODE, MESENTERIC	N	N	N	N	N	N	N	N	N	N
SKELETAL MUSCLE	N	N	N	N	N	N	N	N	N	N
SCIATIC NERVE	N	N	N	N	N	N	N	N	N	N
RECTUM	N	N	N	N	N	N	N	N	N	N
TESTES	N	N	N	N	N	N	N	N	N	N
EPIDIDYMIS	N	N	N		N	N	N	N	N	N
Inflammation, chronic	-	-	-	1	-	-	-	-	-	-
SEMINAL VESICLE	N	N	N	N	N	N	N	N	N	N
EAR	N	N	N	N	N	N	N	N	N	N
FEMUR	N	N	N	N	N	N	N	N	N	N
STERNUM	N	N	N	N	N	N	N	N	N	N
BONE MARROW	N	N	N	N	N	N	N	N	N	N
EYE	N	N	N	N		N	N	N		N
Inflammation, subacute, periorbital	-	-	-	-	1	-	-	-	1	-

THIS PAGE REVISED

study no. 176

R S Morrissey 9/28/95
signature date

See Reports Code Table for Symbol Definitions

25-SEP-1995

PATHOLOGY ASSOCIATES INTERNATIONAL
FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD RATS
TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 176

TABULATED ANIMAL DATA

STUDY ID : TRL SN 176
FATE: ALL

STUDY NUMBER: SN176
GROUP: 4
SEX: MALE

ANIMAL ID:	361	362	363	364	365	366	367	368	369	370
LACRIMAL GLAND	N	N	N		N	N	N	N	N	
Inflammation, chronic	-	-	-	1	-	-	-	-	-	1
LYMPH NODE, MANDIBULAR										
Hemorrhage	-	1	-	-	-	-	-	-	-	-
Hyperplasia, lymphoid	-	-	-	-	-	-	2	-	-	-

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THIS PAGE REVISED

study no. 176

R L Morrissey 9/28/95
signature date

25-SEP-1995

PATHOLOGY ASSOCIATES INTERNATIONAL
FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD RATS
TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 176

TABULATED ANIMAL DATA

STUDY ID : TRL SN 176 STUDY NUMBER: SN176
FATE: ALL GROUP: 1
SEX: FEMALE

ANIMAL ID:	311	312	313	314	315	316	317	318	319	320
BRAIN	N	N	N	N	N	N		N	N	
Dilatation, ventricle	-	-	-	-	-	-	1	-	-	1
PITUITARY GLAND	N	N	N	N	N	N	N	N	N	N
CERVICAL CORD	N	N	N	N	N	N	N	N	N	N
THYMUS	N		N	N	N	N	N	N	N	N
Hemorrhage, multifocal	-	1	-	-	-	-	-	-	-	-
SALIVARY GLAND	N	N	N	N	N	N	N	N	N	N
PANCREAS	N	N	N	N		N	N	N	N	N
Hyperplasia, islet cell	-	-	-	-	1	-	-	-	-	-
MID-THORACIC CORD	N	N	N	N	N	N	N	N		N
Chromatolysis, neuron	-	-	-	-	-	-	-	-	1	-
ADRENAL GLAND		N		N	N	N	N			
Ectopic adrenal	1	-	-	-	-	-	-	-	1	-
Hypertrophy, cortex, multifocal	1	-	1	-	-	-	-	1	1	1
LUMBAR CORD	N	N	N	N	N	N	N	N	N	N
THYROID GLAND	N	N	N	N	N	N	N	N	N	N
PARATHYROID GLAND	N	N	N	U	N	N	N	N	U	N
TRACHEA	N	N	N	N	N	N	N	N	N	N
ESOPHAGUS	N	N	N	N	N	N	N	N	N	N
HEART	N				N		N			

THIS PAGE REVISED

study no. 176

R E Morrissey 9/28/95
signature date

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PATHOLOGY ASSOCIATES INTERNATIONAL
FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD RATS
TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 176

TABULATED ANIMAL DATA

STUDY ID : TRL SN 176
FATE: ALL

STUDY NUMBER: SN176
GROUP: 1
SEX: FEMALE

ANIMAL ID:	311	312	313	314	315	316	317	318	319	320
HEART	N				N		N			
Inflammation, chronic, multifocal	–	1	1	1	–	1	–	1	1	1
AORTA	N	N	N	N	N	N	N	N	N	N
DUODENUM	N	N	N	N	N	N	N	N	N	N
COLON	N	N	N	N	N	N	N	N	N	N
STOMACH	N	N	N	N	N	N	N	N	N	N
LIVER			N	N						
Inflammation, chronic, multifocal	1	1	–	–	1	1	1	1	1	1
SPLEEN	N	N	N	N	N	N	N	N	N	N
JEJUNUM	N	N	N	N	N	N	N	N	N	N
LUNG							N	N		
Mineralization, intrinsic artery	1	–	–	–	–	–	–	–	–	1
Inflammation, acute, perivascular	1	1	2	1	1	1	–	–	–	2
Inflammation, chronic, interstitium	–	1	–	–	–	–	–	–	–	–
Inflammation, pyogranulomatous, focal	–	1	1	–	1	1	–	–	1	–
Hemorrhage	–	–	–	–	1	–	–	–	1	–
KIDNEY			N							
Inflammation, chronic, cortex	–	1	–	–	1	–	1	–	–	–
Nephropathy, progressive	1	1	–	–	–	–	–	1	–	–
Mineralization	2	2	–	1	1	1	1	2	1	1
URINARY BLADDER	N	N	N	N	N	N	N	N	N	N
SKIN (EXPOSURE AREA)				N					N	
Hyperkeratosis	1	1	1	–	1	1	1	1	–	1
Acanthosis	–	–	–	–	–	1	–	–	–	–

THIS PAGE REVISED

See Reports Code Table for Symbol Definitions

study no. 176

RS Morrissey 9/28/95
signature date

25-SEP-1995

PATHOLOGY ASSOCIATES INTERNATIONAL
FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD RATS
TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 176

TABULATED ANIMAL DATA

STUDY ID : TRL SN 176
FATE: ALL

STUDY NUMBER: SN176
GROUP: 1
SEX: FEMALE

ANIMAL ID:	311	312	313	314	315	316	317	318	319	320
SKIN (NON-EXPOSURE AREA)	N		N	N	N	N	N	N	N	N
Hyperkeratosis	-	1	-	-	-	-	-	-	-	-
MAMMARY GLAND	N	N	N	N	N	N	N	N	N	N
ILEUM	N	N	N	N	N	N	N	N	N	N
CECUM	N	N	N	N	N	N	N	N	N	N
LYMPH NODE, MESENTERIC	N	N	N	N	N	N	N	N	N	N
SKELETAL MUSCLE	N	N	N	N	N	N	N	N	N	N
SCIATIC NERVE	N	N	N	N	N	N	N	N	N	N
RECTUM	N	N	N	N	N	N	N	N	N	N
OVARY	N	N	N	N	N	N	N	N	N	N
UTERUS	N	N	N		N					N
Dilatation	-	-	-	1	-	3	1	2	3	-
VAGINA	N	N	N	N	N	N	N	N	N	N
EAR	N	N	N	N	N	N	N	N	N	N
FEMUR	N	N	N	N	N	N	N	N	N	N
STERNUM	N	N	N	N	N	N	N	N	N	N
BONE MARROW	N	N	N	N	N	N	N	N	N	N
EYE	N	N	N	N	N	N			N	
Inflammation, subacute, periorbital	-	-	-	-	-	-	1	1	-	1

THIS PAGE REVISED

study no. 176

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signature date

See Reports Code Table for Symbol Definitions

PATHOLOGY ASSOCIATES INTERNATIONAL
FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD RATS
TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 176

TABULATED ANIMAL DATA

STUDY ID : TRL SN 176 STUDY NUMBER: SN176
FATE: ALL GROUP: 1
SEX: FEMALE

ANIMAL ID:	311	312	313	314	315	316	317	318	319	320
LACRIMAL GLAND	N	N		N		N	N	N	N	N
Inflammation, chronic	-	-	1	-	1	-	-	-	-	-
LYMPH NODE, MANDIBULAR										
Hyperplasia, lymphoid	-	-	-	-	2	-	-	-	-	-
Accumulation, plasma cell	-	2	-	-	-	-	-	-	-	-

THIS PAGE REVISED

study no. 176

See Reports Code Table for Symbol Definitions

RF Morrissey 9/28/95
signature date

PATHOLOGY ASSOCIATES INTERNATIONAL
FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD RATS
TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 176

TABULATED ANIMAL DATA

STUDY ID : TRL SN 176 STUDY NUMBER: SN176
FATE: ALL GROUP: 2
SEX: FEMALE

ANIMAL ID:	331	332	333	334	335	336	337	338	339	340
KIDNEY						N	N			N
Cyst	1	-	-	-	-	-	-	-	-	-
Inflammation, chronic, cortex	1	-	1	1	-	-	-	-	-	-
Nephropathy, progressive	-	-	-	1	-	-	-	-	-	-
Mineralization	1	2	-	1	1	-	-	1	1	-
SKIN (EXPOSURE AREA)	N	N			N	N	N		N	N
Hyperkeratosis	-	-	1	1	-	-	-	1	-	-
SCIATIC NERVE	N	N	N	N	N	N	N	N	N	N
EAR	N	N	N	N	N	N	N	N	N	N
LYMPH NODE, MANDIBULAR										
Hyperplasia, lymphoid	-	-	-	2	-	-	-	-	-	-

THIS PAGE REVISED

study no. 176

RL Morrissey 9/28/95
signature date

See Reports Code Table for Symbol Definitions

25-SEP-1995

PATHOLOGY ASSOCIATES INTERNATIONAL
FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD RATS
TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 176

TABULATED ANIMAL DATA

STUDY ID : TRL SN 176
FATE: ALL

STUDY NUMBER: SN176
GROUP: 3
SEX: FEMALE

ANIMAL ID:	351	352	353	354	355	356	357	358	359	360
SALIVARY GLAND	N									
KIDNEY				N						
Dilatation, pelvis	1	-	-	-	-	-	-	-	-	-
Inflammation, chronic, cortex	-	-	-	-	-	1	-	-	-	1
Nephropathy, progressive	-	1	1	-	-	-	-	-	-	-
Mineralization	-	1	-	-	1	-	1	1	1	1
SKIN (EXPOSURE AREA)	N	N	N			N		N	N	
Hyperkeratosis	-	-	-	1	1	-	1	-	-	1
SCIATIC NERVE	N	N	N	N	N	N	N	N	N	N
EAR	N	N	N	N	N	N	N	N	N	N
LYMPH NODE, MANDIBULAR										
Hyperplasia, lymphoid	-	3	-	-	-	-	-	-	-	-
Accumulation, plasma cell	-	2	-	-	-	-	-	-	-	-

THIS PAGE REVISED

study no. 176

See Reports Code Table for Symbol Definitions

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signature date

PATHOLOGY ASSOCIATES INTERNATIONAL
FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD RATS
TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 176

TABULATED ANIMAL DATA

STUDY ID : TRL SN 176 — STUDY NUMBER: SN176
FATE: ALL — GROUP: 4
SEX: FEMALE

ANIMAL ID:	371	372	373	374	375	376	377	378	379	380
BRAIN	N	N		N	N	N	N		N	
Dilatation, ventricle	-	-	1	-	-	-	-	1	-	1
PITUITARY GLAND	N	N	N	N	N	N	N	N	N	N
CERVICAL CORD	N	N	N	N	N	N	N	N	N	N
THYMUS	N		N	N	N	N	N		N	
Hemorrhage, multifocal	-	1	-	-	-	-	-	1	-	1
SALIVARY GLAND	N	N	N	N	N	N	N		N	N
Inflammation, chronic	-	-	-	-	-	-	-	1	-	-
PANCREAS	N	N	N	N	N	N	N	N		N
Atrophy, acinar	-	-	-	-	-	-	-	-	1	-
MID-THORACIC CORD	N	N	N	N	N	N	N	N	N	N
ADRENAL GLAND	N			N	N	N	N	N		
Hypertrophy, cortex, multifocal	-	1	1	-	-	-	-	-	1	1
LUMBAR CORD	N	N	N	N	N	N	N	N	N	N
THYROID GLAND	N	N	N	N	N	N	N	N	N	N
PARATHYROID GLAND	N	N	N	U	N	N	N	N	N	U
TRACHEA	N	N	N	N	N	N	N	N	N	N
ESOPHAGUS	N	N	N	N	N	N	N	N	N	N
HEART		N	N	N		N		N		
Inflammation, chronic, multifocal	1	-	-	-	1	-	1	-	1	2
AORTA	N	N	N	N	N	N	N	N	N	N

THIS PAGE REVISED

study no. 176

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signature date

See Reports Code Table for Symbol Definitions

PATHOLOGY ASSOCIATES INTERNATIONAL
FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD RATS
TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 176

TABULATED ANIMAL DATA

STUDY ID : TRL SN 176
FATE: ALL

STUDY NUMBER: SN176
GROUP: 4
SEX: FEMALE

ANIMAL ID:	371	372	373	374	375	376	377	378	379	380
DUODENUM	N	N	N	N	N	N	N	N	N	N
COLON	N	N	N	N	N	N	N	N	N	N
STOMACH	N	N	N	N	N	N	N	N	N	N
LIVER			N							N
Inflammation, chronic, multifocal	1	1	-	1	1	1	1	1	1	-
SPLEEN	N	N	N	N	N	N	N	N	N	N
JEJUNUM	N	N	N	N	N	N	N	N	N	N
LUNG		N				N				
Mineralization, intrinsic artery	-	-	-	1	-	-	-	-	1	-
Inflammation, acute, perivascular	-	-	1	1	1	-	1	1	1	-
Inflammation, chronic, interstitium	-	-	-	-	-	-	1	-	-	-
Inflammation, pyogranulomatous, focal	1	-	1	1	1	-	-	1	-	1
Hemorrhage	-	-	-	-	1	-	-	1	1	1
KIDNEY		N								
Inflammation, chronic, cortex	1	-	-	-	1	1	1	1	1	-
Nephropathy, progressive	-	-	-	1	-	1	-	-	-	1
Mineralization	-	-	1	1	1	1	1	-	2	1
URINARY BLADDER	N	N	N	N	N	N	N	N	N	N
SKIN (EXPOSURE AREA)					N		N			
Hyperkeratosis	1	1	1	1	-	1	-	1	1	1
Acanthosis	1	-	-	-	-	1	-	2	1	-
SKIN (NON-EXPOSURE AREA)	N	N	N	N	N	N	N	N	N	N
MAMMARY GLAND	N	N	N	N	N	N	N	N	N	N

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study no. 176

RS Morrissey 9/28/95
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25-SEP-1995

PATHOLOGY ASSOCIATES INTERNATIONAL
FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD RATS
TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 176

TABULATED ANIMAL DATA

STUDY ID : TRL SN 176
FATE: ALL

STUDY NUMBER: SN176
GROUP: 4
SEX: FEMALE

ANIMAL ID:	371	372	373	374	375	376	377	378	379	380
LEUM	N	N	N	N	N	N	N	N	N	N
ECUM	N	N	N	N	N	N	N	N	N	N
YMPH NODE, MESENTERIC	N	N	N	N	N	N	N	N	N	N
KELETAL MUSCLE	N	N	N	N	N	N	N	N	N	N
CIATIC NERVE	N	N	N	N	N	N	N	N	N	N
ECTUM	N	N	N	N	N	N	N	N	N	N
VARY	N	N	N	N	N	N	N	N	N	N
TERUS	N		N	N	N	N	N	N	N	N
Dilatation	-	2	-	-	-	-	-	-	-	-
AGINA	N	N	N	N	N	N	N	N	N	N
AR	N	N	N	N	N	N	N	N	N	N
EMUR	N	N	N	N	N	N	N	N	N	N
TERNUM	N	N	N	N	N	N	N	N	N	N
ONE MARROW	N	N	N	N	N	N	N	N	N	N
YE	N	N			N	N		N		
Inflammation, subacute, periorbital	-	-	2	1	-	-	1	-	1	2
ACRIMAL GLAND	N	N	N	N	N		N			N
Inflammation, chronic	-	-	-	-	-	1	-	1	1	-

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SECTION V

CORRELATION OF GROSS AND MICROSCOPIC (MICRO) FINDINGS

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FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD RATS
TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 176

CORRELATION OF GROSS & MICRO

STUDY ID : TRL SN 176
FATE: ALL

STUDY NUMBER: SN176
GROUP: 1
SEX: MALE

Animal ID: 301
Animal Fate: Scheduled sacrifice

Reference to Necropsy Record:	Related Histopathology:
THYMUS - LESION, MOTTLED	THYMUS - Hemorrhage, multifocal

Animal ID: 306
Animal Fate: Scheduled sacrifice

Reference to Necropsy Record:	Related Histopathology:
THYMUS - LESION, MOTTLED	THYMUS - Hemorrhage, multifocal

Animal ID: 307
Animal Fate: Scheduled sacrifice

Reference to Necropsy Record:	Related Histopathology:
LYMPH NODE, MANDIBULAR - LESION, 4 MM X 2 MM, RED	LYMPH NODE, MANDIBULAR - Hemorrhage

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9/28/95
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PATHOLOGY ASSOCIATES INTERNATIONAL
FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD RATS
TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 176

CORRELATION OF GROSS & MICRO

STUDY ID : TRL SN 176
FATE: ALL

STUDY NUMBER: SN176
GROUP: 2
SEX: MALE

Animal ID: 321
Animal Fate: Scheduled sacrifice

eference to Necropsy Record:
YMPH NODE, MANDIBULAR - ENLARGED, 5 MM X 12 MM

Related Histopathology:
LYMPH NODE, MANDIBULAR - Hyperplasia, lymphoid

Animal ID: 326
Animal Fate: Scheduled sacrifice

eference to Necropsy Record:
YE - RIGHT, PIGMENTATION, RED

Related Histopathology:
EYE - Hemorrhage, periorbital

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PATHOLOGY ASSOCIATES INTERNATIONAL
FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD RATS
TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 176

CORRELATION OF GROSS & MICRO

STUDY ID : TRL SN 176
FATE: ALL

STUDY NUMBER: SN176
GROUP: 3
SEX: MALE

Animal ID: 341
Animal Fate: Scheduled sacrifice

Reference to Necropsy Record:
LYMPH NODE, MANDIBULAR - LESION, 2 MM X 3 MM, RED

Related Histopathology:
LYMPH NODE, MANDIBULAR - Hemorrhage

THIS PAGE REVISED
study no. 176
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9/28/95
date

PATHOLOGY ASSOCIATES INTERNATIONAL
FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD RATS
TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 176

CORRELATION OF GROSS & MICRO

STUDY ID : TRL SN 176
FATE: ALL

STUDY NUMBER: SN176
GROUP: 4
SEX: MALE

Animal ID: 362
Animal Fate: Scheduled sacrifice

eference to Necropsy Record:	Related Histopathology:
YMPH NODE, MANDIBULAR - LESION, 4 MM X 2 MM, RED	LYMPH NODE, MANDIBULAR - Hemorrhage
DRENAL GLAND - LEFT, FOCUS, RED	ADRENAL GLAND - Hypertrophy, cortex, multifocal

Animal ID: 367
Animal Fate: Scheduled sacrifice

eference to Necropsy Record:	Related Histopathology:
YMPH NODE, MANDIBULAR - ENLARGED, 9 MM X 7 MM	LYMPH NODE, MANDIBULAR - Hyperplasia, lymphoid

THIS PAGE REVISED

study no. 176

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PATHOLOGY ASSOCIATES INTERNATIONAL
FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD RATS
TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 176

CORRELATION OF GROSS & MICRO

STUDY ID : TRL SN 176
FATE: ALL

STUDY NUMBER: SN176
GROUP: 1
SEX: FEMALE

Animal ID: 312
Animal Fate: Scheduled sacrifice

Reference to Necropsy Record:
LYMPH NODE, MANDIBULAR - ENLARGED, 8 MM X 5 MM

Related Histopathology:
LYMPH NODE, MANDIBULAR - Accumulation, plasma cell

Animal ID: 315
Animal Fate: Scheduled sacrifice

Reference to Necropsy Record:
LYMPH NODE, MANDIBULAR - ENLARGED, 7 MM X 13 MM

Related Histopathology:
LYMPH NODE, MANDIBULAR - Hyperplasia, lymphoid

Animal ID: 319
Animal Fate: Scheduled sacrifice

Reference to Necropsy Record:
EYE - LEFT, LESION, OPAQUE

Related Histopathology:
EYE - No corresponding lesion

THIS PAGE REVISED

study no. 176

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PATHOLOGY ASSOCIATES INTERNATIONAL
FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD RATS
TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 176

CORRELATION OF GROSS & MICRO

STUDY ID : TRL SN 176
FATE: ALL

STUDY NUMBER: SN176
GROUP: 2
SEX: FEMALE

Animal ID: 334
Animal Fate: Scheduled sacrifice

eference to Necropsy Record:
YMPH NODE, MANDIBULAR - ENLARGED, 7 MM X 7 MM

Related Histopathology:
LYMPH NODE, MANDIBULAR - Hyperplasia, lymphoid

THIS PAGE REVISED

study no. 176

R L Tornincasa 9/28/95
signature date

PATHOLOGY ASSOCIATES INTERNATIONAL
FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD RATS
TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 176

CORRELATION OF GROSS & MICRO

STUDY ID : TRL SN 176
FATE: ALL

STUDY NUMBER: SN176
GROUP: 3
SEX: FEMALE

Animal ID: 351
Animal Fate: Scheduled sacrifice

Reference to Necropsy Record:
SALIVARY GLAND - LESION, RED

Related Histopathology:
SALIVARY GLAND - No corresponding lesion

Animal ID: 352
Animal Fate: Scheduled sacrifice

Reference to Necropsy Record:
LYMPH NODE, MANDIBULAR - ENLARGED, 7 MM X 12 MM

Related Histopathology:
LYMPH NODE, MANDIBULAR - Hyperplasia, lymphoid

THIS PAGE REVISED

study no. 176

R8 Morrissey 9/28/95
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PATHOLOGY ASSOCIATES INTERNATIONAL
FOUR WEEK TOXICITY STUDY OF WR279396
AFTER DAILY DERMAL APPLICATION IN CD RATS
TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 176

CORRELATION OF GROSS & MICRO

STUDY ID : TRL SN 176
FATE: ALL

STUDY NUMBER: SN176
GROUP: 4
SEX: FEMALE

No Gross Observations for any animal in this group

THIS PAGE REVISED
study no. 176
signature
7/28/95
date

SECTION VI

QUALITY ASSURANCE STATEMENT

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study no. 176

ignature 9-28-95 date

QUALITY ASSURANCE STATEMENT

This histopathology project was inspected and audited by the PAI Quality Assurance Unit (QAU) as required by the Good Laboratory Practice (GLP) standards promulgated by the U.S. Food and Drug Administration. The pathology narrative report is an accurate reflection of the recorded data. The following table is a record of the inspections/audits performed and reported by the QAU:

	Date of Inspection	Phase Inspected	Date Findings Reported to Management and Study Pathologist
*	05/31/95	Tissue Trimming	06/01/95
*	04/27/95	Processing/Embedding	04/27/95
**	04/06/95	Microtomy	04/06/95
*	04/27/95	Staining	04/27/95
*	04/27/95	Coverslipping	04/27/95
*	01/05/95	Labeling	01/05/95
*	04/06/95	Quality Control/Checkout	04/06/95
**	06/14/95	Individual Animal Data	06/14/95
**	06/14/95	Computer Generated Tables	06/14/95
**	06/14/95	Draft Pathology Report	06/14/95
**	09/13/95	Final Pathology Report	09/13/95
**	09/28/95	Amended Final Pathology Report	09/28/95

* General quarterly phase inspection
** Inspection specific for this study

In accordance with the PAI Quality Assurance Division's Standard Operating Procedures, all critical phase inspections are conducted on a random basis quarterly or more frequently. Those general phase inspections listed are the most recent conducted during the period each task associated with this project was performed.

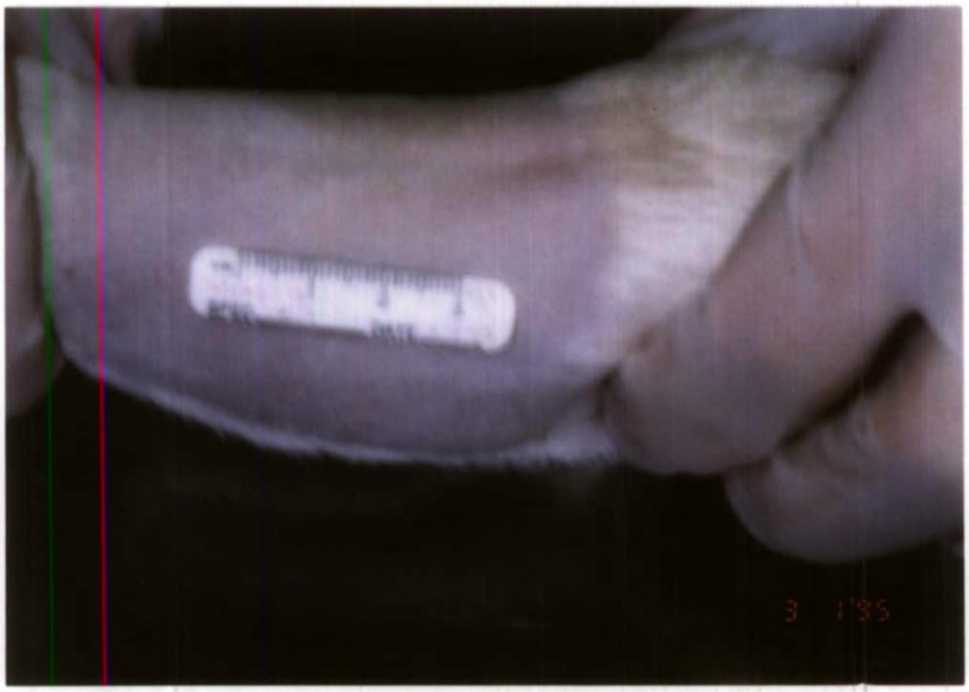
Andrea M. Smith
Quality Assurance Unit
PAI Illinois Division

09/28/95
Date

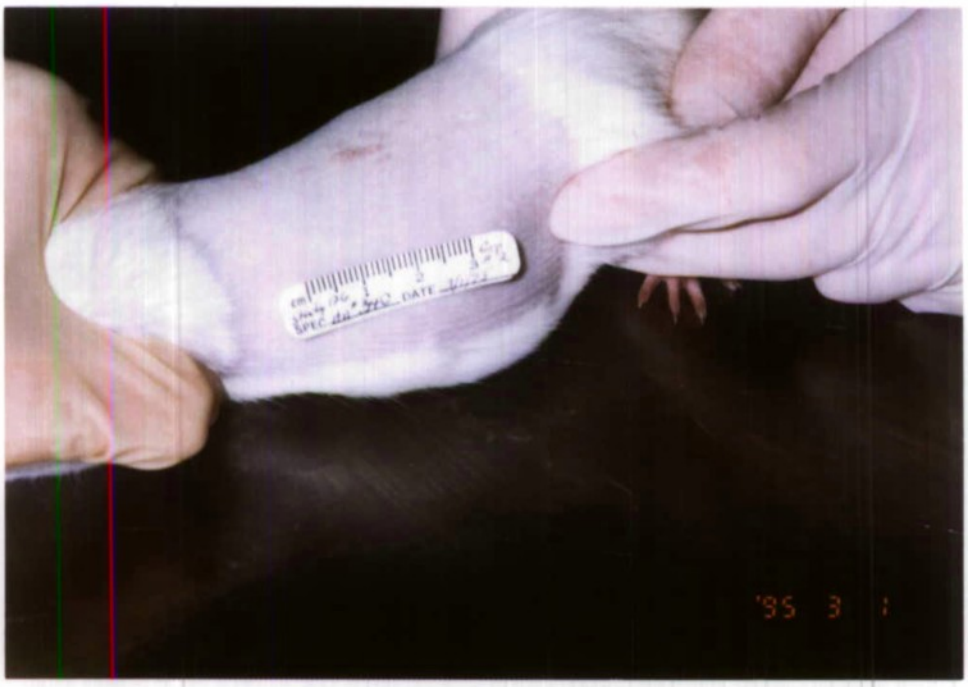
Four Week Toxicity Study of WR279396 After Daily Dermal Application in CD® Rats
UIC/TRL Study Number 176

APPENDIX 10

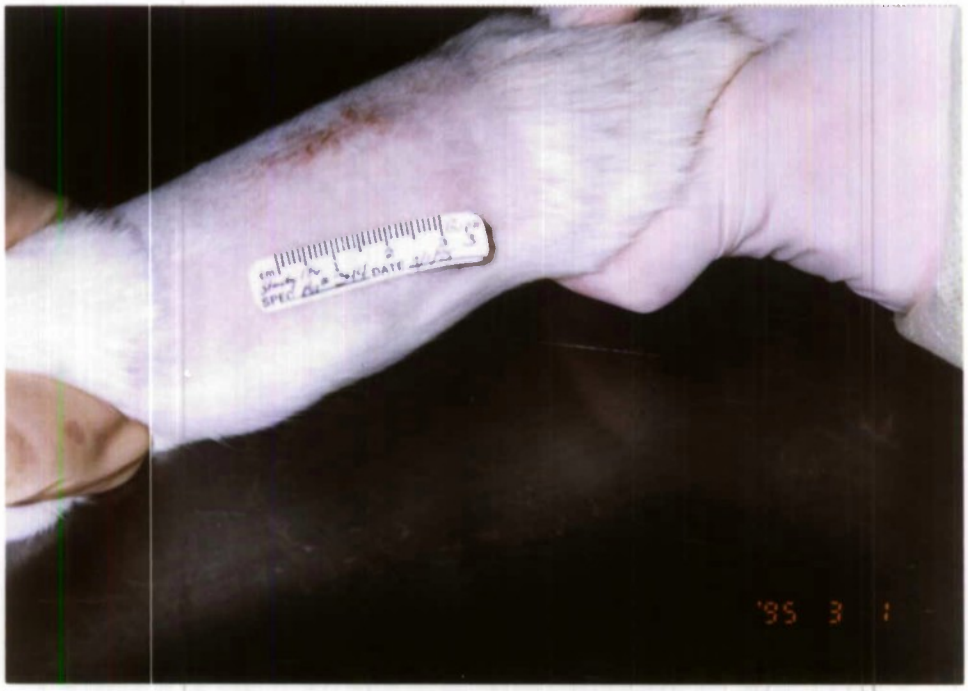
PHOTOGRAPHS OF TREATMENT SITES ON DAY 6



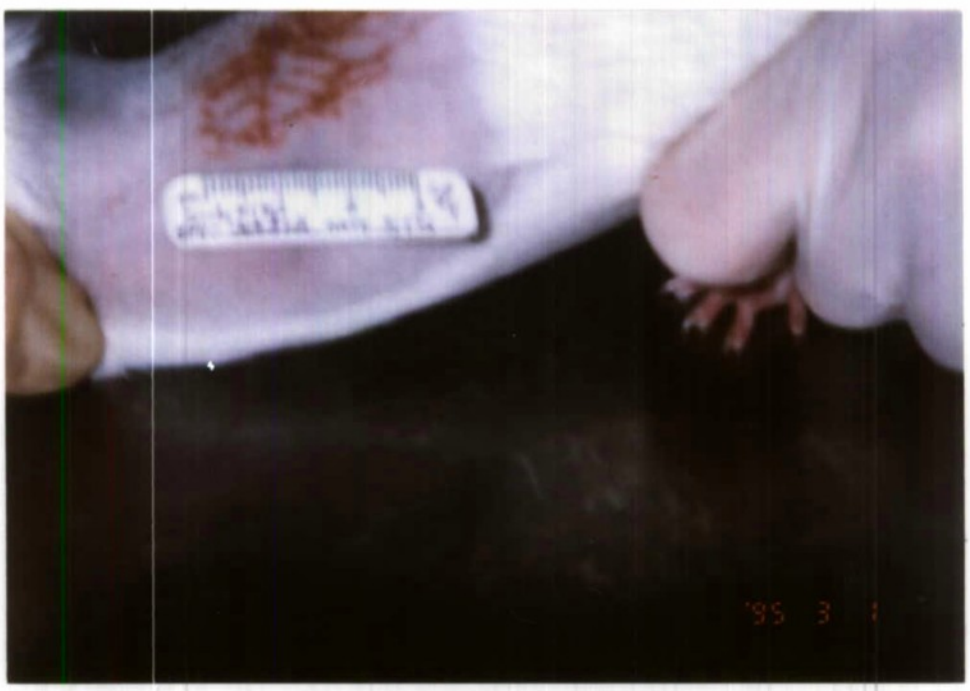
Study Day: 6
Animal No.: 313 Sex: Female
Dosing Volume: 1.67 ml/kg/day x 2 Vehicle Control



Study Day: 6
Animal No.: 340 Sex: Female
Dosing Volume: 0.07 ml/kg/day x 2 WR279396



Study Day: 6
Animal No.: 344 Sex: Male
Dosing Volume: 0.33 ml/kg/day x 2 WR279396



Study Day: 6
Animal No.: 372 Sex: Female
Dosing Volume: 1.67 ml/kg/day x 2 WR279396

APPENDIX 11

PROTOCOL AND PROTOCOL AMENDMENTS

Contract No.: DAMD17-92-C-2001
Task Order No.: UIC-12A
UIC/TRL Study No.: 176

FOUR WEEK TOXICITY STUDY OF WR279396 AFTER DAILY DERMAL APPLICATION IN CD® RATS

1.0 PURPOSE OF THE STUDY:

The objective of this study is to determine the local and systemic (organ) toxicity of WR279396 in CD® rats following four weeks of daily dermal application. WR279396 (Iowa Formulation 232) is a cream containing 0.5% gentamicin sulfate and 15% paromomycin sulfate, which is being developed for use against cutaneous leishmaniasis. The protocol for this study was approved by the UIC Animal Care Committee (Appendix 1).

2.0 SPONSOR:

2.1	Name:	U.S. Army Medical Materiel Development Activity
2.2	Address:	Fort Detrick Frederick, MD 21702-5009
2.3	Representative:	George J. Schieferstein, Ph.D.

3.0 TESTING FACILITY:

3.1	Name:	Toxicology Research Laboratory (TRL)
3.2	Address:	University of Illinois at Chicago (UIC) Department of Pharmacology 1940 W. Taylor St. Chicago, Illinois 60612-7353
3.3	Study Director:	Barry S. Levine, D.Sc., D.A.B.T.

4.0 DATES:

4.1	Proposed Initiation of Dosing:	02/23/95
4.2	Proposed Necropsy Dates:	03/23-24/95
4.3	Proposed Study Completion Date (Draft Study Report):	06/23/95

REVISED PAGE
STUDY NO: 176 INITIAL: BJ
DATE: 9/21/95

5A.0 TEST ARTICLE

5A.1 Name or Code No: WR279396 [0.5% gentamicin sulfate- and 15% paromomycin sulfate-containing cream (Iowa Formulation 232)]

5A.2 TRL Chemical No: 1980614

5A.3 Physical Description: White cream. The specific gravity is ≈1.0, as indicated by the Sponsor.

5A.4 Stability and Handling of Test Article:

5A.4.1 Storage Conditions to Maintain Stability:

5A.4.1.1 Temperature: 2 - 8°C.

5A.4.1.2 Humidity: Ambient conditions at 2 - 8°C.

5A.4.1.3 Light: Protect from light; opaque bottle.

5A.4.1.4 Special Requirements: None.

5A.4.2 Special Handling Procedures: Standard safety precautions including gloves, eye protection, mask and labcoat.

5A.4.3 Log of Test Article: The amount, date, identity of person(s) removing aliquots and the purpose for which each aliquot of the test article was removed from the batch will be documented. At termination of the study, all unused test article will be returned to the Sponsor if requested.

5B.0 PLACEBO (VEHICLE)

5B.1 Name or Code No: Iowa Formulation 232 without either gentamicin sulfate or paromomycin sulfate (vehicle).

5B.2 TRL Chemical No: 1990614

5B.3 Physical Description: White cream. The specific gravity is ≈1.0, as indicated by the Sponsor.

5B.4 Stability and Handling of Placebo (Vehicle):

5B.4.1 Storage Conditions to Maintain Stability:

REVISED PAGE
STUDY NO: 176 INITIAL: BL
DATE: 9/21/95

5B.4.1.1 Temperature: 2 - 8°C.

5B.4.1.2 Humidity: Ambient conditions at 2 - 8°C.

5B.4.1.3 Light: Protect from light; opaque bottle.

5B.4.1.4 Special Requirements: None.

5B.4.2 Special Handling Procedures: Normal safety procedures will be used including labcoats, masks, eye protection, and gloves.

5B.4.3 Log of Placebo (Vehicle): The amount, date, identity of person(s) removing aliquots and the purpose for which each aliquot of the control article was removed from the batch will be documented. At termination of the study, all unused control article will be returned to Sponsor if requested.

6.0 PERSONNEL:

Study Director	Barry S. Levine, D.Sc., D.A.B.T.
Toxicologist	Clyde W. Wheeler, Ph.D.
Pathologist	Robert L. Morrissey, D.V.M., Ph.D., D.A.C.V.P.
Clinical Veterinarian	James Artwohl, D.V.M., M.S., D.A.C.L.A.M.
Veterinarian Support	Documented in the raw data
Ophthalmologist	Samuel J. Vainisi, D.V.M., D.A.C.V.O.
Clinical Laboratory	Maria Lang, A.H.T., C.V.T.
Tox. Lab Supervisor	Soudabeh Soura, B.S.
Lead Technician	Documented in raw data
Quality Assurance	Ronald C. Schoenbeck

7.0 TEST SYSTEM:

7.1	Species:	Rat
7.2	Strain:	CD® (Virus Antibody Free)
7.3	No. and Sex(s):	40 males and 40 females
7.4	Age of Animals:	Approximately 7 weeks old at dosing initiation.
7.5	Weight of Animals:	Approximately 200 - 250 g (males) and approximately 175 - 200 g (females) at dosing initiation.

REVISED PAGE
STUDY NO: 176 INITIAL: BSL
DATE: 9/21/95

7.6 Source of Animals: Charles River Breeding Laboratories. Kingston, NY.

7.7 Justification for Selection of Test System: The FDA requires the use of two animal species in preclinical toxicology studies. The rat is a standard and accepted rodent species for toxicology studies, and is specified by the Sponsor.

7.8 Procedure for Unique Identification of Test System: Upon arrival, each animal will be given a study-unique quarantine/pretest number. During the test animal selection process, each test animal will be assigned a test animal number unique to it within the population making up the study. This number will appear as an ear tag and will also be coded on a subcutaneously implanted microchip. It will also appear on a cage card visible on the front of each cage. The cage card will additionally contain the study number, test article identification, treatment group number, sex and dose level. Cage cards will be color-coded as a function of treatment group. Raw data records and specimens will also be identified by the unique test animal number.

7.9 Housing: The animals will be housed in an AAALAC-accredited facility. Animals will be singly housed in polycarbonate cages with Anderson-bed-a-cob bedding (Heinold, Kankakee, Illinois) in a temperature (65-78°F) and humidity (30-70%) controlled room with a 14 hour light/10 hour dark cycle. The cage size, 840 cm^2 area and 20 cm height, is adequate to house rats at the upper weight range as described in the *Guide for the Care and Use of Laboratory Animals*, DHHS (NIH) No. 86.23. All animals will be routinely transferred to clean cages with fresh bedding once weekly.

7.10 Quarantine Procedure: Animals will be quarantined for approximately one week. During that time, the animals will be observed daily for signs of illness, and all unusual observations will be reported to the Study Director, Toxicologist or Clinical Veterinarian. Animals will be examined during quarantine and approved for use by the Clinical Veterinarian prior to being placed on test. Any sickly animals will be eliminated prior to the test animal selection process. If a selected animal appears sickly prior to initiation of treatment, it will be replaced by a healthy animal prior to initiation of treatment under the direction of the Study Director or Toxicologist. Quarantine release will be documented on the Clinical Veterinarian Log by the veterinarian prior to study initiation.

7.11 Food: Certified Rodent Chow No. 5002 (PMI, Inc., St. Louis, MO) will be provided *ad libitum* from arrival until termination.

7.12 Water: Tap water from an automatic watering system in which the room distribution lines are flushed daily will be provided *ad libitum* from arrival until termination. The water is not treated with additional chlorine or HCl.

7.13 There are no known contaminants in the feed or water which are expected to influence the study. A copy of the feed certification will be kept with the study records. The results of the most current comprehensive chemical analyses of Chicago water are documented in files maintained by Quality Assurance.

REVISED PAGE
STUDY NO: 176 INITIAL: AL
DATE: 3/14/95

8.0 EXPERIMENTAL DESIGN:

8.1 Treatment Groups:

Treatment Group	Treatment	Paromomycin Dose Level (mg/kg/day)	Gentamicin Dose Level (mg/kg/day)	Dosing Volume (ml/kg/day)	Number of Males	Number of Females
1	Vehicle	0	0	1.67 x 2 (1.67)	10	10
2	WR279396	20 (10)	0.7 (0.04)	0.07 x 2 (0.07)	10	10
3	WR279396	100 (50)	3.3 (1.7)	0.33 x 2 (0.33)	10	10
4	WR279396	500 (250)	16.7 (8.4)	1.67 x 2 (1.67)	10	10

Dose levels were selected following discussions with the Sponsor. They were chosen on the basis of the amount of paromomycin which will be administered to patients although both paromomycin and gentamicin will be administered. As indicated by the Sponsor, the intended routine clinical dose of paromomycin is 5 mg/kg/day. As such, a low dose in this study of 20 mg/kg/day allows for a four-fold margin of safety. It was further stated by the Sponsor that the maximum clinical dose for a severely infected individual would be 50 mg/kg/day. Accordingly, the present mid dose affords a two-fold safety factor over this worst case scenario clinical dose. The high dose level in this study of 500 mg/kg/day (1.67 ml WR279396/kg/application) is intended to result in toxicity and is near the typical upper limit of dermal dosing of 2 ml/kg/application.

Because moderate to severe erythema was seen in high and mid dose animals on day 5, the initial dose levels were reduced by one-half. The new dose levels of paromomycin and gentamicin are shown above in parentheses. This will be accomplished by reducing the frequency of dosing from twice daily to once daily. The dosing volume per application will remain constant.

The number of animals 10/sex/group, is necessary for adequate statistical analysis, and is routinely used in rodent regulatory toxicology studies. This number of animals is also indicated in the 1993 *OECD Guidelines for Testing of Chemicals;* Repeated Dose Dermal Toxicity: 21/28 Day Study. No such FDA document exists for the testing of drugs.

8.2 Frequency and Route of Administration of the Test Article: The FDA requires toxicology testing for at least twice the duration of clinical testing to support a Phase III clinical trial of WR279396 which will be clinically tested against cutaneous leishmaniasis for no more than 10 days. The current 28-day dermal toxicology study will provide the clinicians with a 4-day safety net in case the duration of clinical treatment must be extended.

The test article will be applied by the dermal route twice daily for four weeks. The fur

REVISED PAGE
STUDY NO: 176 INITIAL:
DATE: 3/24/95

on the back of each test animal will be clipped approximately 24 hours prior to initial test article application. An area approximately 7 cm long and extending approximately 3 cm on both sides of the midline will be exposed, and will constitute the dosing area. Only animals with healthy intact skin will be used. The backs will be reshaved during the course of the study as necessary.

The animals will be fitted with a jacket for dermal applications during week -1. Immediately prior to the initial treatment on day 0 and weekly thereafter unless fissuring is observed, the animals will have the dosing area abraded by cross-hatched cuts made with a detached size 10 electric clipper blade so that the stratum corneum is penetrated but the dermis is left intact. The test article will be administered using a 1 ml tuberculin syringe (0.01 ml graduations) and uniformly applied as a thin film over the exposure area of the skin (up to $\approx$ 10% of the total body surface area) twice daily, approximately 3 - 4 hours apart, for at least 28 consecutive days. The specific volume to be administered (to the nearest 0.01 ml) will be adjusted on the basis of each animal's most recent body weight. The material will be initially applied to a latex gloved finger, which will be used to uniformly apply the test article to the exposure area of the skin. A separate gloved finger will be used for each animal, i.e. after dosing up to four rats, the glove will be discarded, and a new latex glove will be donned. The application site will be left uncovered. Approximately 3 - 4 hours after the last daily application, the exposure site will be wiped with a water-moistened paper towel and the animal jackets will be removed and left off overnight. The animals will be dosed up to and including the day prior to scheduled necropsy on day 28 or 29.

8.3 Justification of Route: Dermal application is the intended clinical route and is specified by the Sponsor.

8.4 Procedure to Control Bias during the Assignment of Animals to Treatment Groups: During the quarantine/pretest period, the animals will be randomized separately by sex into the groups shown in Section 8.1 using a computer-generated randomization procedure on the basis of body weight.

8.5 Test Article Dosage Form Preparation and Analyses: The test article will be administered undiluted. Homogeneity, stability and test article concentration analyses will not be conducted by UIC/TRL, and are the responsibility of the Sponsor.

8.6 Type and Frequency of Observations, Tests, Analyses and Measurements:

8.6.1 Clinical Signs: All animals will be observed twice daily $\approx$ 1 - 2 hours after each dermal application for clinical signs of toxicity. Additionally, all animals will be observed for moribundity/mortality in the morning.

8.6.2 Clinical Observations: All animals will be subjected to a physical examination including examination of eyes and all orifices at randomization (Week -1), on day 0 and weekly thereafter.

REVISED PAGE
NO: 176 INITIAL: RJL
DATE: 31/4/95

8.6.3 Evaluation of Dermal Irritation: Dermal irritation will be evaluated once weekly prior to the first daily dose. The draize dermal irritation scoring procedure will be employed (Draize, J.H., 1965; Appraisal of the Safety of Chemicals in Foods, Drugs, and Cosmetics; Association of Food and Drug Officials of the U.S., Austin, TX).

Erythema and eschar formation:

No erythema	0
Very slight erythema (barely perceptible)	1
Well defined erythema	2
Moderate to severe erythema	3
Severe erythema (beet redness) to slight eschar formation (injuries in depth)	4

Edema formation:

No edema	0
Very slight edema (barely perceptible)	1
Slight edema (edges of area well defined by definite raising)	2
Moderate edema (raised approximately 1.0 mm)	3
Severe edema (raised more than 1.0 mm and extending beyond the exposure area)	4

8.6.4 Body Weight: Body weights of all animals will be recorded at randomization in week -1, on day 0 and weekly thereafter.

8.6.5 Food Consumption: Food consumption for all animals will be measured weekly commencing in week -1.

8.6.6 Clinical Pathology: Hematology and clinical chemistry parameters will be measured on days 27 and 28 (one day prior to necropsy). The animals will be anesthetized by inhalation of CO_2:O_2 (80:20), and approximately 1.5 - 2.0 ml of blood will be collected from the orbital sinus to measure the following parameters. The samples will be processed in the same random order as collected.

REVISED PAGE
STUDY NO: 176 INITIAL:
DATE: 3/14/95

Hematology

Erythrocyte count and morphology	Mean corpuscular volume (MCV)
Hematocrit	Mean corpuscular hemoglobin (MCH)
Hemoglobin	Mean corpuscular hemoglobin concentration (MCHC)
Leukocyte count, total and differential	Platelet count
	[a]Reticulocyte count

[a]Slides will be prepared, but will not be evaluated unless signs of anemia are present.

Clinical Chemistry

Alanine aminotransferase (ALT)	Glucose
Albumin	Globulin (calc.)
Alkaline phosphatase	Phosphorus, inorganic
Bile acids, total	Potassium
Calcium	Protein, total
Chloride	Sodium
Cholesterol	Sorbitol dehydrogenase
Creatinine	Urea nitrogen (BUN)

8.6.7 Ophthalmologic Examinations: All animals will be examined by indirect ophthalmoscopy prior to study initiation and in week 4.

8.6.8 Pathology: All animals which die on test or are sacrificed if moribund will be necropsied on the day of death. Surviving animals will be killed and necropsied in random order on days 28 and 29. Animals will be anesthetized by Metofane® inhalation (Pitman-Moore, Mundelein, IL) and will then be perfused transcardially with saline followed by 10% neutral buffered formalin (NBF). An extensive necropsy will then be performed under the direction and supervision of the pathologist. Terminal body weights will be collected prior to routine sacrifice.

The necropsy procedure will be a thorough and systematic examination and dissection of the animal viscera and carcass, and collection and fixation of the following tissues/organs in 10% neutral buffered formalin.

REVISED PAGE
STUDY NO: 176 INITIAL: RJL
DATE: 3/14/95

*Adrenal glands
Aorta
*Brain
Cecum
Colon
Duodenum
Ears (including sensory hair cells of *crista ampullaris*, cochlear and vestibular hair cells, and middle and inner ear)
Epididymides
Esophagus
Eyes
Femur with bone marrow
Gross lesions
*Heart
Ileum
Jejunum
*Kidneys (including proximal tubules of the cortex)
Lacrimal gland (exorbital)
*Liver
*Lung/Bronchi
Lymph node (mesenteric)
Mammary gland
*Ovaries
Pancreas
Pituitary
Prostate
Rectum
Salivary gland (submandibular)
Sciatic nerve
Seminal vesicles
Skeletal muscle (thigh)
Skin (exposure and non-exposure areas)
Spinal cord (cervical, mid-thoracic and lumbar)
*Spleen
Sternum with bone marrow
Stomach
*Testes
Thymus
Thyroid gland with parathyroids
Trachea
Urinary bladder
Uterus
Vagina

*Weighed at scheduled necropsy (paired organs will be weighed as a unit).

All tissues collected at necropsy will be examined microscopically in all control and high dose animals. In addition, animals found dead or subjected to a moribund kill may be processed for microscopic examination following consultation with the Sponsor. All gross lesions will be examined microscopically. The kidneys, ears and sciatic nerve, and any other target organs identified in high dose animals, will be examined in low and mid dose animals.

8.6.9 Statistical Analyses: For each sex, Analysis of Variance tests will be conducted on body weight, food consumption, hematology, clinical chemistry and organ weight data. Organ weight analyses will consider weights relative to brain

REVISED PAGE
STUDY NO: 176 INITIAL:
DATE: 3/4/95

weight. If a significant F ratio is obtained ($p \leq 0.05$), Dunnett's t test will be used for pairwise comparisons to the control group. Frequency data such as incidence of mortality, gross necropsy observations and tissue morphology observations will be compared by Fishers Exact Test or Chi-square analyses as necessary.

8.6.10 Deliverables: Quantitative data will be tabulated and presented in the report. In addition to the written report, individual data in "ASCII" form and summary data tables of parameters and variability will be transmitted to the Sponsor on magnetic media (computer diskette). The transcribed data on disk will no longer be considered GLP compliant.

9.0 RECORDS TO BE MAINTAINED:

All data generated during the conduct of the study, except those that are generated as direct computer input, will be recorded directly, promptly, and accurately in ink in bound books with prenumbered pages or on worksheets that will be bound during or at the conclusion of the nonclinical laboratory study. All appropriate computer and machine output will be bound during or at the conclusion of the study. All data entries will be dated on the day of entry and signed or initialed by the person entering the data.

Any changes in entries for whatever reason (e.g., to correct an error or transposition) will be made so as not to obscure the original entry, will indicate the reason for such change, and will be dated and signed or identified at the time of data input. In computer driven collection systems, the operator responsible for direct data input will be identified at the time of data input. Any changes in computer entries for whatever reason (e.g., to correct an error or transposition) will be made in such a manner so as not to obscure the original entry, if possible, will indicate the reason for such change, and will be dated and the responsible individual will be identified.

All recorded data will be reviewed, signed, and dated by a knowledgeable person, other than the person making the entry, to assure adherence to procedures and to verify observations.

Upon completion of the study and submission of the final report, all raw data, documentation, specimens (including histology and paraffin blocks of tissues) and other materials necessary to reconstruct the study will be stored in the TRL Archives maintained by Quality Assurance, unless otherwise specified by the Sponsor.

All changes or revisions, and reasons therefore, to this protocol once it is approved will be documented, signed by the Study Director and Sponsor, dated and maintained with the protocol. Additionally, the Sponsor is to be notified immediately of any illness or problems which develop during the study. Should a protocol or SOP deviation occur, the circumstances, action taken (if any), and the impact on the study will be assessed immediately by the Study Director and documented on a Protocol Deviation form.

10.0 REGULATORY REQUIREMENTS:

This study will be performed in compliance with the UIC/TRL Quality Assurance Program designed to conform with FDA Good Laboratory Practice Regulations and EPA Good Laboratory Practice Standards.

Will this study be submitted to a regulatory agency? Yes
If so, to which agency(ies)? US Food and Drug Administration
Does the Sponsor request that remaining test and control articles be returned?
Possibly; see Sections 5A.4.3 and 5B.4.3
Does the Sponsor request that samples of the test article/carrier mixture(s) be sent to the Sponsor for analysis? Not applicable

11.0 PROTOCOL APPROVAL:

STUDY DIRECTOR: Barry S. Levine, D.Sc., D.A.B.T. — Date: 10/28/94

QUALITY ASSURANCE: Ronald Schoenbeck — Date: 10/28/94

SPONSOR APPROVAL: George Schieferstein, Ph.D., Contracting Officer's Representative (COR) — Date: 10/31/94.

COMMENTS FROM THE COR:

UIC The University of Illinois at Chicago

Office of the Vice Chancellor for Research (M/C 672)
310 Administrative Office Building
1737 West Polk Street
Chicago, Illinois 60612-7227
(312) 996-4995

Contract No.: DAMD17-92-C-2001
Task Order No.: UIC-12A
UIC/TRL Study No.: 176

Appendix 1

October 27, 1994

Barry S. Levine
Pharmacology
312 BGRC, M/C 868

Dear Dr. Levine:

The modifications requested in your correspondence of October 20, 1994 pertaining to your approved protocol ACC: #93-031-19: "Four Week Dermal Toxicity Study of WR279396 in CD Rats" have been reviewed in accordance with the Animal Care and Use Policies of the University of Illinois at Chicago. You will be pleased to know that the modifications were approved on October 26, 1994 and consequently the records of Animal Care Committee will be revised to reflect these changes.

Thank you for complying with the Animal Care Policies and Procedures of UIC.

Sincerely yours,

Michael W. Levine, Ph.D.
Chair, Animal Care Committee

MWL:st
xc: BRL

PROTOCOL AMENDMENT

Study No.: 176

Title: Four Week Dermal Toxicity Study of WR279396 in CD® Rats

1. Page 1 Section 4.0

Add the study dates as follows:

4.1	Proposed Initiation of Dosing:	02/23/95
4.2	Proposed Necropsy Dates:	03/23-24/95
4.3	Proposed Study Completion Date (Draft Study Report):	6/23/95

Reason: The study dates have been finalized.

2. Page 2 Section 5B.3

Include the physical description of the control article as a "White cream. The specific gravity is $\approx$ 1.0, as indicated by the Sponsor."

Reason: Physical description provided by the Sponsor upon receipt of the control article.

3. Page 4 Section 7.8

Replace the third sentence with the following: "This number will appear as an ear tag and will also be coded on a subcutaneously implanted microchip. It will also appear on a cage card visible on the front of each cage."

Reason: Clarification of the protocol. We have recently implemented the use of an implantable microchip identification system for use in GLP toxicology studies.

4. Page 5 Section 8.1

Add the redlined text to the table and insert the following paragraph after first paragraph.

PROTOCOL AMENDMENT

Study No.: 176

Title: Four Week Dermal Toxicity Study of WR279396 in CD® Rats

4. (contd.)

Treatment Group	Treatment	Paromomycin Dose Level (mg/kg/day)	Gentamicin Dose Level (mg/kg/day)	Dosing Volume (ml/kg/day)	Number of Males	Number of Females
1	Vehicle	0	0	1.67 x 2 (1.67)	10	10
2	WR279396	20 (10)	0.7 (0.04)	0.07 x 2 (0.07)	10	10
3	WR279396	100 (50)	3.3 (1.7)	0.33 x 2 (0.33)	10	10
4	WR279396	500 (250)	16.7 (8.4)	1.67 x 2 (1.67)	10	10

Because moderate to severe erythema was seen in high and mid dose animals on day 5, the initial dose levels were reduced by one-half. The new dose levels of paromomycin and gentamicin are shown above in parentheses. This will be accomplished by reducing the frequency of dosing from twice daily to once daily. The dosing volume per application will remain constant.

Reason: Because moderate to severe erythema was seen in mid and high dose animals on day 5, following consultation with the Sponsor, the dose levels were reduced by one-half as described above.

5. Page 6 Section 8.2

In the last paragraph, indicate that the jackets will be removed and left off the animals overnight following cleaning of the exposure site after the last daily application.

Reason: Clarification of the protocol.

6. Page 7 Section 8.6.6

Change when blood will be collected for the measurement of clinical pathology parameters to "days 27 and 28 (one day prior to necropsy)" from "at scheduled termination on days 28 and 29".

Reason: Clarification of the protocol. Logistics prevent the performance of blood collection for clinical pathology determinations and the whole animal perfusion for tissue fixation on the necropsy day.

PROTOCOL AMENDMENT

Study No.: 176

Title: Four Week Dermal Toxicity Study of WR279396 in CD® Rats

7. Page 8 Section 8.6.8

Replace the first paragraph with the following: "All animals which die on test or are sacrificed if moribund will be necropsied on the day of death. Surviving animals will be killed and necropsied in random order on days 28 and 29. Animals will be anesthetized by Metofane® inhalation (Pitman-Moore, Mundelein, IL) and will then be perfused transcardially with saline followed by 10% neutral buffered formalin (NBF). An extensive necropsy will then be performed under the direction and supervision of the pathologist. Terminal body weights will be collected prior to routine sacrifice."

Reason: The means of euthanasia was changed and transcardial perfusion with NBF was added to insure the proper fixation of the neural tissues.

8. Page 9 Section 8.6.8

A. Remove "Bone marrow smear (femur)" from tissue list.

B. Remove reference to bone marrow smears in first paragraph and delete second paragraph.

Reason: Because the animals are being whole body perfused with 10% neutral buffered formalin at necropsy, bone marrow smears can not be obtained.

Approvals:

STUDY DIRECTOR: _____ 3/14/95
Barry S. Levine, D.Sc. D.A.B.T. Date

SPONSOR APPROVAL: _____ 3/15/95.
George J. Schieferstein, Ph.D. Date
Contracting Officer's
Representative (COR)

PROTOCOL AMENDMENT

Study No.: 176

Title: Four Week Dermal Toxicity Study of WR279396 in CD® Rats

9. Page 1 Title

Change the Study Title to "FOUR WEEK TOXICITY STUDY OF WR279396 AFTER DAILY DERMAL APPLICATION IN CD® RATS" from "FOUR WEEK DERMAL TOXICITY STUDY OF WR279396 IN CD® RATS".

Reason: Sponsor requested change in the protocol and in the resulting study report.

10. Page 2 Section 5B.0

Change the designation of the Iowa Formulation 232 cream without either gentamicin sulfate or paromomycin sulfate to "PLACEBO (VEHICLE)" from "CONTROL ARTICLE".

Reason: Sponsor requested change in the protocol and in the resulting study report.

11. Page 2 Section 5B.4

Replace "Stability and Handling of Control Article" with "Stability and Handling of Placebo (Vehicle)".

Reason: Sponsor requested that the Iowa Formulation 232 cream without either gentamicin sulfate or paromomycin sulfate be designated as the "Placebo (Vehicle)".

12. Page 2 Section 5B.4.3

Replace "Log of Control Article" with "Log of Placebo (Vehicle)".

Reason: Sponsor requested that the Iowa Formulation 232 cream without either gentamicin sulfate or paromomycin sulfate be designated as the "Placebo (Vehicle)".

Approvals:

STUDY DIRECTOR: Barry S. Levine, D.Sc. D.A.B.T. — Date: 9/21/95

SPONSOR APPROVAL: George J. Schieferstein, Ph.D. Contracting Officer's Representative (COR) — Date: 9/20/95

APPENDIX 12

STUDY DEVIATIONS

Contract No.: DAMD17-92-C-2001
Task Order No.: UIC-12A
UIC/TRL Study No.: 176

FOUR WEEK TOXICITY STUDY OF WR279396 AFTER DAILY DERMAL APPLICATION IN CD® RATS

Study Deviations*

Deviation Type	Specific Deviation	Effect on Study
Protocol	On a few occasions, the temperature and/or relative humidity deviated outside the specified ranges in the animal room. The temperature and relative humidity deviations ranged from -2 to +2°F and -3 to +0%, respectively, outside the specified ranges.	None. These deviations were sporadic.
Protocol	Reticulocyte count was determined in the absence of signs of anemia.	None.
Protocol	Animals were anesthetized by inhalation of CO_2:O_2 (70:30) instead of CO_2:O_2 (80:20).	None.
Protocol	Parathyroids (7) and mammary gland (1) were not evaluated histologically in a few high dose and control animals. Parathyroids and mammary glands are inherently difficult to obtain in sections because of their size. These tissues were recorded as "unsuitable for complete evaluation" since they were missing in both the original section and in the recut and retrim attempts to obtain them.	None. Treatment-related lesions were not seen in these tissues.

*The detailed "Deviation Reports" are contained in the raw data which are archived at the Toxicology Research Laboratory , University of Illinois at Chicago, Department of Pharmacology, 1940 W. Taylor St., Chicago, Illinois 60612.

The above deviations did not affect the integrity of the study.

Barry S. Levine, D.Sc., D.A.B.T.

10/3/95
Date